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Clinical Section

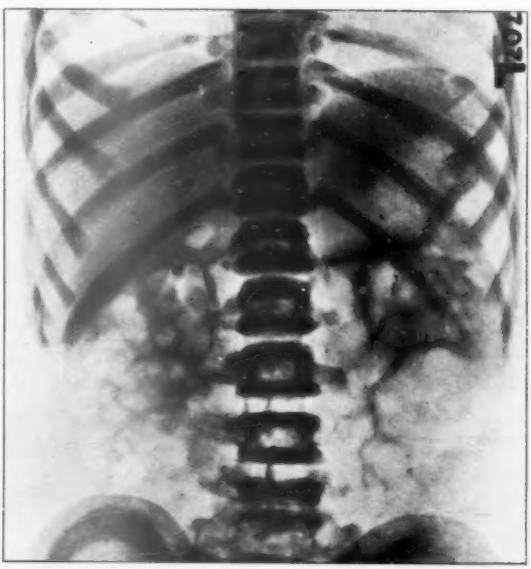
President—DUNCAN FITZWILLIAMS, C.M.G., F.R.C.S.

[*November* 11, 1938, ***continued***]

Marble Bones: Albers-Schönberg's Disease.—H. H. LANGSTON, F.R.C S. (for Sir HENRY GAUVAIN).

Helen R., aged 10.

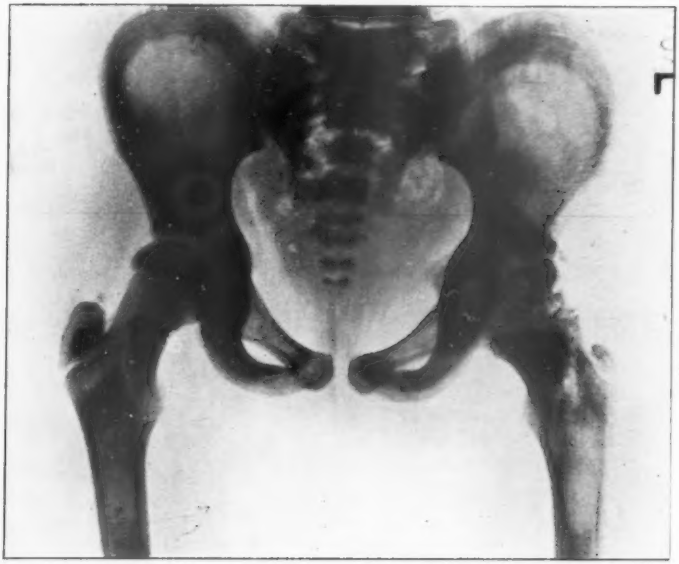
When aged 6 years was admitted to Lord Mayor Treloar Cripples' Hospital, Alton, with septic arthritis of the left hip, of eleven weeks' duration and secondary to osteomyelitis of the femoral neck. She had been acutely ill at the onset of the osteomyelitis, had previously undergone—at another hospital—an operation in



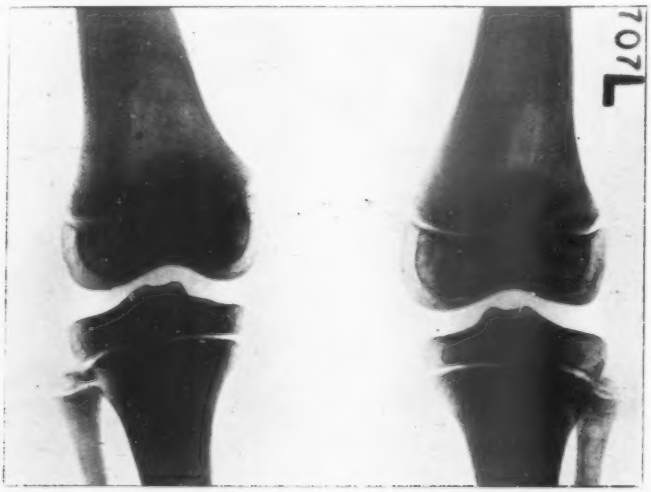
Spine—illustrating variation in density of deposit at successive growth periods.

which the neck of the femur was guttered and the joint opened. She was transferred to the Treloar Hospital eleven weeks later.

On admission.—General condition good, apart from that of the left hip, in which there were still discharging sinuses ; no abnormality was noted on clinical examination. The spleen was not palpable. A skiagram, however, showed in addition to



Pelvis and femora—note lines of varying density illustrating varying deposit of calcium at successive growth periods.



Knee-joints—note the "halo" appearance produced by recently formed bone being less dense than that previously formed.

the changes of septic arthritis and osteomyelitis, bands of unusual density running through the ilium, and corresponding patches in the femora. Skiagrams were, therefore, taken of the whole skeleton, and showed what appeared to be well-marked changes due to Albers-Schönberg disease.

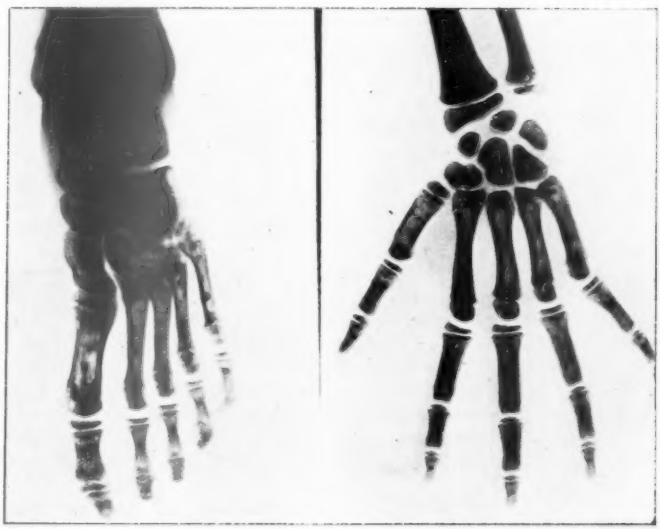
Special investigations.—Blood calcium, 12·8 mgm. per 100 c.c., blood phosphorus 5·6 mgm. per 100 c.c.

Blood count: 4,500,000 cells (normal); Hb. 75%; C.I. 0·83. W.B.C. 11,800. *Differential:* Polys. 70%; eosinos. 3·7%: lymphos. 25%; monos. 1·3%.

Blood sigma reaction negative. Blood phosphatase not measured.

Ophthalmic surgeon's report: No evidence of optic atrophy.

Family history.—On X-ray examination no abnormalities were detected in the skeleton of the child's father or of her two brothers; suggestive patches of increased density were noted in the mother's skeleton but these were much less marked than the changes in the child. The mother has always enjoyed good health, but she has a sister who has suffered from "anæmia for years." No skiagrams of this sister have yet been obtainable.



Foot and hand—note circular deposits in tarsus and carpus and linear deposits in the long bones.

Progress.—The disease in the left hip and femur followed an uneventful course and healing took place without further operative interference. The patient was discharged on 11.7.35, eighteen months after admission.

Since then she has been kept under observation and skiagrams have been taken at approximately yearly intervals. These show bands and patches of abnormally dense bone in the pelvis, femora, and vertebral bodies, and rings of dense bone in the carpal and tarsal bones. The increased density is most obvious in the diaphyseal regions of the long bones and in the epiphyses. In the shafts of the long bones the patches of increased density have a peculiar flame-shaped appearance in certain bones.

Blood-count (July, 1938): R.B.C. 4,000,000; Hb. 73%; C.I. 0·91; W.B.C. 10,500. *Differential*: Polys. 41·5%; eosinos. 2%; basos. 0·2%; large lymphos. 20·5%; small lymphos. 27·5%; monos. 8·3%.

Slight anisocytosis. A few red cells show punctate basophilia.

Sedimentation rate: First hour, 4 mm., second hour, 4 mm., third hour, 4 mm., fourth hour, 3 mm.

Symmetrical Swellings at the Angles of the Jaw: for Diagnosis.—A. E. MORTIMER WOOLF, F.R.C.S.

The patient, a woman aged 28, thinks there has been some enlargement at both angles of the jaw since birth, but for the last five or six years this has increased. There is no pain but she is somewhat distressed on account of her appearance.

On examination.—At each angle of the jaw there is a soft swelling, which appears to be in the masseter muscle. On deep palpation of the jaw a spur can be felt arising from the lower border in the region of each angle of the mandible, the presence of the spur is definitely confirmed by X-rays, but it is difficult to obtain a satisfactory picture.

The PRESIDENT said the feel of these tumours was so cyst-like that he would feel inclined to put in a big needle and see if they contained fluid. If they proved to be solid perhaps some tissue could be withdrawn in the needle and examined.

Congenital Hemiplegia with Mental Deficiency, treated by Dorsal and Lumbar Sympathectomy.—LAWRENCE ABEL, M.S.

E. K., a girl aged 6 years and 6 months.

History.—Case of congenital right hemiparesis, with subnormal mentality and incontinence of urine and fæces. Parents healthy. Older child normal. Referred from doctor for possible improvement by sympathectomy. Right arm and right leg always cold and blue and chilblains frequent. Skin temperature tests demonstrated a considerable degree of vasospasm in the right arm and right leg, and sympathectomy was therefore advocated.

Operations.—18.1.38: Right lumbar ganglionectomy. Second and third right lumbar ganglia removed. Marked improvement in warmth and colour of the limb followed. Patient free the whole winter from chilblains in right foot.

22.3.38: Right upper dorsal sympathectomy performed. One inch of dorsal lumbar chain removed with second dorsal ganglia. Marked improvement in warmth and colour of right upper extremity and striking change for the better in patient's mental condition.

Subsequent history.—Next day patient sat up and was bright and cheerful, playing with toys and talking to other children—in contradistinction to dull, uninterested, lethargic mentality before the operation. School teacher now reports an all-round improvement in intelligence. Incontinence of urine and fæces has ceased, except for occasional nocturnal enuresis (about once a week).

? Double Buccal Carcinoma.—LAWRENCE ABEL, M.S.

Mr. H. S., aged 59.

History.—Six weeks: Ulcer of left upper jaw; three weeks: ulcer of left lower jaw.

On examination.—Teeth foul. Leukoplakia on inner side of left cheek. Two typical epitheliomatous ulcers are present. In the upper jaw there is one 2·5 cm. by 1 cm., at the back of the left upper alveolus, the other, 1 cm. diameter, almost opposite on the left lower alveolus. Both were found to be squamous-celled carcinoma. There is an enlarged left submaxillary lymphatic gland.

Congenital Pyloric Stenosis with Cardio-stenosis in a Child aged 4 days. —BERNARD SCHLESINGER, F.R.C.P.

History.—Normal delivery. From birth the child vomited everything, even water, and appeared to be in great discomfort after feeding, which seemed to embarrass

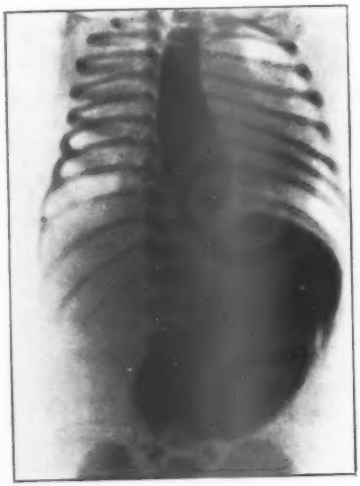


FIG. 1.

FIG. 2.

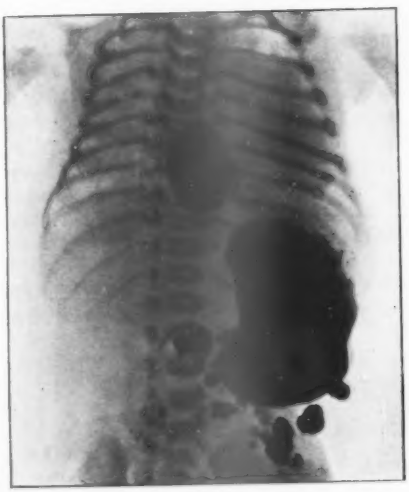


FIG. 3.

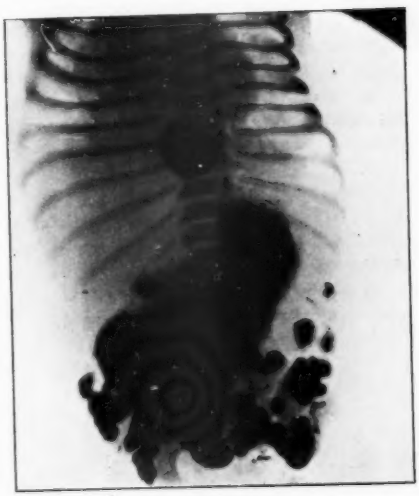


FIG. 4.

A series of skiagrams of a barium swallow taken at ¾ hour, 5, 19 and 30 hours respectively.

respiration. Urine passed normally; meconium began to become fæcal on the fourth day. After a feed no peristalsis was visible and a tumour was not felt.

Treated with stomach wash-out and eumydrine but continued to vomit. Wash-out caused some distress and cyanosis.

Temperature rose to 105° F. and signs of pneumonia developed. Meanwhile X-ray photographs of a barium meal were taken and showed a marked cardiospasm, a greatly enlarged stomach, and much residue after nineteen hours; some still present after thirty-six hours.

The child died of pneumonia, despite treatment in oxygen tent.

Post-mortem report: Much dilated œsophagus with thickened walls and a definite thickening at the cardiac orifice. Stomach: Greatly dilated, with thin wall; muscular hypertrophy at the pylorus. Lungs: Widespread bronchopneumonia.

Histological examination showed typical hypertrophy of sphincter muscle at pylorus and also of circular layer of muscle fibres at cardiac end of œsophagus.

Actinomycosis of the Jaw.—B. SANGSTER SIMMONDS, M.S.

Alfred W., aged 30, labourer.

Seen first in Out-Patients Department (Mr. A. Simpson-Smith) on 5.4.38 complaining of (1) swelling on left jaw near posterior end of zygomatic arch (one week); (2) stiffness and pain in left temporo-mandibular joint region; (3) swollen gland by angle of left jaw (three weeks).

History of present condition.—Ten days ago a left lower molar tooth had been removed at St. Mary's Hospital. After this the swelling had become larger and more painful and the left side of the face hot and swollen. The size of the swelling varied, but did not increase on eating.

Past history.—Gonorrhœa three months ago; now symptomless.

Condition on admission (5.4.38).—Tense, hot, tender, red swelling, limited above by the temporal fascia, below by the lower margin of the jaw, behind by the ear, and anteriorly by the orbital margin. The gland behind the angle of the jaw was not palpable as a separate swelling. Trismus very marked. Teeth foul.

A blood-count revealed a leucocytosis. Wassermann and Kahn reactions negative. Skiagram of jaw: No abnormality detected. A diagnosis of parotid abscess was decided on.

8.5.38: An incision was made along the line of the zygoma, ¼ in. below its lower margin. Some sero-sanguineous fluid was obtained and when examined for organisms was found to contain only pus cells and diphtheroids.

12.5.38: Dental condition investigated by Mr. S. F. St. J. Steadman, and $\frac{123\ 5\ 78}{345}$ removed.

The patient was treated with heat and analgesics and later the swelling was re-incised, but no mycelia were found. He was also seen by the V.D. department, with a view to excluding a gonococcal joint.

19.5.38: Now complained of deafness in left ear for one week and was examined by Ear, Nose and Throat Department, but nothing was found locally to account for this other than spread of inflammatory process. X-ray examination of sinuses and jaw negative. Wassermann and Kahn reactions negative.

27.5.38: Pus from sinus showed colonies of actinomycosis.

7.6.38: Readmitted and treated with ½ grm. of prontosil t.d.s. The swelling had increased so that it involved the left eyelids.

A blood-count showed secondary anæmia and leucocytosis.

1.7.38: Doses of prontosil increased: 1 grm. four times daily for six days, then

1 grm. three times daily for seven days, alternating with a like quantity of uleron each day, then ½ grm. daily for seven days. At the same time deep X-ray therapy was given in small daily doses for three weeks. The patient became somewhat cyanosed at the beginning but there was no leucopenia, nor was there sulph- or methæmoglobin on spectroscopic examination of the blood. After two days' rest, this course was repeated, and the swelling generally appeared less. A pocket of pus which formed by the ramus of the mandible was evacuated, but no actinomyces were found. He complained of pain in the head and arms and palpitations. Discharged from hospital on 8.8.38. There was a little discharge from one sinus and on 14.8.38 he was readmi ted with discharge from a lump behind the ear.

1.9.38 : X-ray therapy was resumed. This caused nausea and digestive upsets, and as the patient became somewhat paler he was given liver extract orally. He was also taking 15 gr., and later 20 gr., of iodide of potassium thrice daily.

21.10.38 : Patient cyanosed and very ill. Two pockets of pus on left forehead and cheek were aspirated and actinomycelia were found.

? Kienböch's Disease.—B. SANGSTER SIMMONDS, M.S.

George C., aged 24, carpenter.

In February 1938 he had fallen on a scaffold and his arm had been put in plaster for a fortnight. Subsequently treated with massage and exercises.

18.7.38 : Seen in Injury Clinic, complaining of pain in wrist and swelling. X-rays showed local bony change, sclerosis of semi-lunar and rarefaction of other carpal bones. Plastered.

17.8.38 : No pain. Further treatment : New plaster ; massage ; radiant heat ; exercises.

29.8.38 : Effusion from the wrist-joint, which was very tender. Treatment : Scott's dressing, elastoplast, and antiphlogistine.

19.10.38 : Patient complains of clicking and pain on extension and flexion.

Vitamin-C Deficiency and Periostitis of Both Ulnæ. ? Scurvy.—RICHARD W. B. ELLIS, M.D.

P. H., a male infant now aged 6½ months, was born at term by forceps delivery, weighing 7 lb. Both parents are healthy and pregnancy was normal ; throughout pregnancy the mother had a good mixed diet containing much fruit and green vegetables. The infant was breast-fed for five days, then put on to half-cream Cow and Gate, which was changed after a short time to a boiled cow's-milk formula and subsequently to humanized Trufood. No orange juice had been given when the infant was first seen (29.8.38) at the age of 4 months, and tomato juice had been given on one or two occasions only. At this time, the baby was brought to the Infants Hospital with a history of poor gain in weight, refusal of feeds, fretfulness, and screaming, of several weeks' duration ; the left forearm had been noticed to be swollen for two days. The forearm had been knocked three weeks previously but no disability noted at the time. Two older children, aged 8 and 4 years, are well ; no miscarriages.

On examination (29.8.38) the infant (aged 4 months) appeared pale and poorly nourished, weighing 11 lb. 3 oz. Both forearms were swollen, the swelling involving the ulnæ throughout their length. There was no œdema of the arms and no swelling or effusion into the wrist or elbow-joints. The limbs were moved freely, and although the infant was extremely fretful, the forearms did not appear acutely tender. No abnormality of legs. No beading of ribs. No hæmorrhages into skin or mucosæ. Spleen and liver not palpable. Physical examination otherwise negative. Temperature normal.

Investigations.—Tourniquet test: No petechiæ produced after three minutes.

Mantoux test: 1 : 1,000 negative.

Urine, 30.8.38: Deposit shows some red blood-cells present. 12.9.38: Deposit shows very occasional leucocytes, and some red blood-cells present. 5.10.38: No red blood-cells present.

Ascorbic acid excretion in urine (Dr. A. G. Signy): 31.8.38: 1·8 mgm. in twenty-four hours (normal 20 to 40 mgm.). 6.9.38: 5·2 mgm. in twenty-four hours. 23.9.38: 1·1 mgm. in twenty-four hours. 10.10.38: 13·9 mgm. in twenty-four hours.

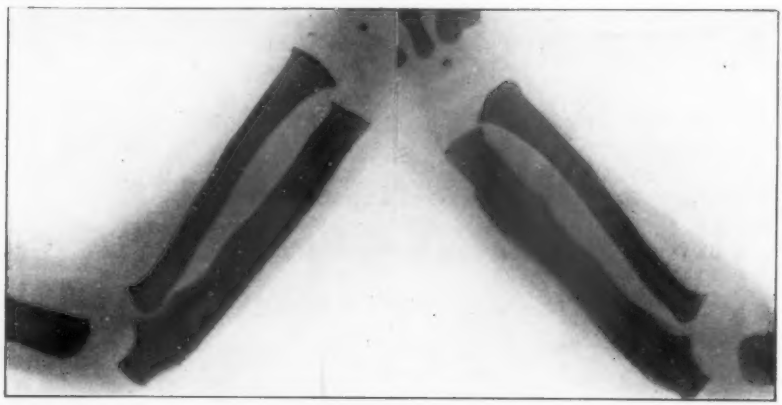


FIG. 1.—29.8.38: Right and left forearms.

Blood examination (31.8.38).—W.B.C. 10,800 per c.mm., polys. 46%; lymphos. 42%; monos. 8%; eosinos. 4%.

Wassermann and Kahn reactions (mother and child) negative.

Gonococcal complement-fixation test (12.9.38) negative.

Radiological examinations (Dr. L. J. Rae).—29.8.38: Marked periostitis along practically the whole length of the shaft of each ulna. No evidence of scurvy or rickets. No abnormality seen in bones of lower limbs. 22.9.38: Increase in amount of periosteal new bone, which is also showing evidence of consolidating. The shaft of the left radius appears to be affected. Legs clear. 17.10.38: Consolidation of the periosteal new bone, the appearances suggesting arrest of the condition and improvement.

Course.—The infant was treated with 2 oz. fresh orange juice daily, which was taken well, and 3 ♏ adexolin b.d. He gained weight slowly on 5½ oz. humanized Trufood four-hourly and was discharged home 26.9.38. He was readmitted a week later for two weeks on account of fretfulness and difficulty in feeding. Temperature did not rise above 99·5° F. throughout period of observation.

Present condition.—Still shows some swelling of the forearms but no other

abnormality. The X-ray changes (17.10.38) suggest arrest of the condition and improvement (fig. 2). The ascorbic acid excretion on October 10 had risen to 13·9 mgm. in twenty-four hours.

Comment.—The diagnosis in this case appeared to be either a low-grade infective periostitis or an atypical scorbutic lesion. Syphilis could be excluded by the negative Wassermann reactions of both mother and child, and the absence of other stigmata. The complement fixation test for gonoccocal infection was negative. Leukæmia was excluded by the blood examination and course. Melorheostosis (to which the earlier X-rays bore some resemblance, and which occasionally affects more than one limb) was negatived by the changes that had taken place in the X-rays during two months. In favour of scurvy, were the facts that the infant was known to have a severe Vitamin C deficiency, that red cells were present in the urine, and that the lesions were bilateral. Against this diagnosis were the unusual site of the lesions, the complete absence of radiological changes of acute scurvy at

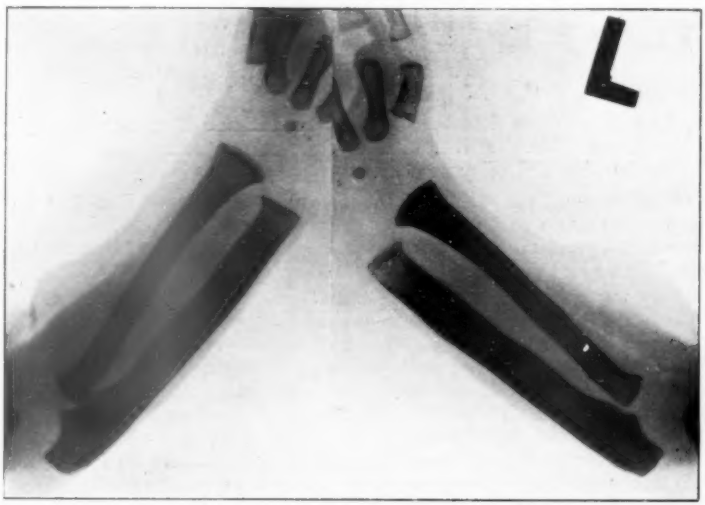


FIG. 2.—17.10.38: Appearance of arrest and healing.

the ends of the long bones (lipping, densely calcified matrix, Trummerfeld zone, &c.), the lower limbs being entirely unaffected, and the age of onset. If scorbutic the condition must presumably have become manifest when the infant was little more than three months of age, since extensive calcification is visible in the X-rays taken at four months; such an early onset is extremely rare in the case of an infant whose mother has been on a high Vitamin C diet throughout the whole of pregnancy.

The diagnosis of periostitis due to a low grade infection, complicating the existing Vitamin C deficiency, is suggested by the X-ray appearances, both positive and negative; the peculiar bilateral distribution is, however, difficult to explain on this basis, and no other convincing evidence of infection was found.

Obliterative Vascular Disease of the Lower Extremities of ? Tuberculous Origin.—GEOFFREY KONSTAM, M.D.

Alice W., aged 31, was referred by Mr. O. T. Dinnick to the West London Hospital on October 15, 1938, complaining of pain and swelling of the legs and feet and ulceration of the right foot.

History.—At the age of 14 the patient had enlarged cervical glands on the right side, and about the same time a swelling appeared on the inner side of the right calf. The glands in the neck were excised, and a diagnosis of tuberculous adenitis was made.

The swelling of the right leg increased in size and numerous swellings appeared on both legs. Three years after their appearance these began to ulcerate. The feet began to swell and walking became painful on account of pain at the site of the ulcers, and aching in the right thigh and leg. The right pre-auricular gland became enlarged and an abscess formed, which was aspirated, and the gland was later excised.

Eight years ago the third toe of the left foot began to ulcerate and finally became gangrenous and was amputated.

Four years ago bilateral lumbar sympathectomy was performed at the Prince of Wales Hospital, Plymouth. Both legs improved, the left more than the right, but a few weeks after discharge from hospital the right foot began to ulcerate, and since then the ulcers have remained in an indolent state.

Family history.—Two sisters died of tuberculosis, one of meningitis, and the other one of peritonitis. One brother died of tuberculous meningitis. Her father and two paternal uncles died of pulmonary tuberculosis.

Condition on examination.—Old operation scars were present on both sides of the neck, and there was a paramedian scar in the lower abdomen. Pulse, temperature, and respiration, were normal. There was no evidence of wasting except in the leg muscles.

The legs were reddish-blue in colour and two indolent ulcers, surrounded by a zone of brown pigmentation, were present on the dorsum of the right foot. Numerous superficial veins—some of which were thrombosed—were seen on both legs. The posterior tibial artery was felt with difficulty in the right leg but not in the left. The lower limbs from the knees downwards were cold. Slight brawny œdema was present in both legs and feet. The oscillometric readings were: Right ankle 2½, left ankle ¾, right wrist 2, left wrist 2. No marked blanching of the limb was noticed on elevation. Brachial blood-pressure, 130/80. The arteries of the upper limbs were not thickened. The heart was not clinically enlarged and the heart sounds were normal. No abnormality was detected in the respiratory, alimentary, or nervous systems.

Investigations.—Skiagrams: Chest, calcified node in the left lower zone; legs, no signs of arterial calcification.

Sedimentation rate 11 mm. in one hour (Westergren). Mantoux reaction (1 : 1,000 old tuberculin) positive. Wassermann reaction, negative.

Comment.—It will be noted that the onset of symptoms in the legs occurred at the same time as the tuberculous adenitis in the neck, when the patient was aged 14. This, coupled with the strong family history of tuberculosis, seems to suggest that obliterative lesions in the veins and arteries of the lower extremities were due to tuberculous endarteritis and phlebitis.

Roger, Gouget and Boiret (1907)[1] quote Bäumler, who described venous and

[1] Maladies des artères et de l'aorte, p. 145, "Traité de Médecine et de Thérapeutique", fasc. xxiv, by Brouardel and Gilbert.

subsequent arterial thrombosis in both lower extremities in a young patient afflicted by tuberculous pleurisy. Histological examination showed tubercles in the walls of the thrombosed arteries.

Dr. PARKES WEBER said the symptoms were those of thrombo-angiitis obliterans, but the fact that the patient was a female and very young, practically excluded that diagnosis. Therefore the vascular disease must be of some other type (such as suggested by Dr. Konstam, or a rare juvenile example of atheromatous disease).

Meningitis, treated with Prontosil.—A. R. DARLOW (for Dr. B. SCHLESINGER). Eileen M., aged 10 months.

3.10.38: Admitted to hospital under the care of Dr. Schlesinger, on account of difficulty in feeding.

Previous history irrelevant.

Present illness.—Onset of diarrhœa three weeks ago, later giving place to constipation. Most feeds have been vomited for about a fortnight. No cold or cough. Physical examination revealed no abnormality.

4.10.38: Stiffness of neck muscles noticed. Lumbar puncture: Protein 320 mgm. Globulin +. Sugar nil. Chlorides 660 mgm. Cells 2,400 (polymorphs). Meningococci (later identified as Group II). 5 c.c. polyvalent serum were given intrathecally and 5 c.c. intramuscularly.

5.10.38: Lumbar puncture repeated, 4 c.c. serum introduced. 10 c.c. given intravenously. Injections of prontosil begun. Two dry lumbar punctures on the next two days. Prontosil given by mouth. Cisternal puncture next day. 4 c.c. Group II serum introduced. (Protein 70 mgm.; globulin negative; chlorides 720 mgm. Sugar present. Cells 167, mainly lymphocytes.)

Uneventful convalescence.

Prontosil dosage:—

First	10	days by injection	10 c.c.	daily	= 100 gr.
For	3	,,	28 gr.	,,	= 84 gr.
,,	7	,,	11 gr.	,,	= 77 gr.
,,	6	,,	7½ gr.	,,	= 45 gr.

Œdema of Leg.—H. L-C. WOOD, M.S.

Mrs. M. W., aged 38. Housewife. One child. One miscarriage.

History.—In May 1937 the patient had diarrhœa and vomiting for three days without ceasing. A diagnosis of "ptomaine poisoning" was made, and she remained in bed for three weeks, still vomiting occasionally. After getting up from bed she noticed that her right foot became swollen. She was told to take exercise, so she played a round of golf, after which her whole leg became œdematous. It remained swollen for three weeks. A diagnosis of "femoral thrombosis" was made. The leg was immobilized, and the swelling almost completely subsided. When she was up and walking it returned, and the limb at times has been red and inflamed and acutely painful.

Present condition.—The right leg is swollen to about twice the size of the left. The swelling extends from the thigh down to the toes. There is no pitting on pressure, and the œdema is of the lymphatic type. No redness, discoloration, or scarring, on leg or thigh, and no enlarged veins. Liver and spleen not enlarged.

Wassermann reaction negative. Blood sedimentation rate 17 mm. (Fahraeus' test).

Discussion.—The PRESIDENT suggested that a Kondoleon operation might be performed.

Mr. SIMPSON-SMITH thought that as the swelling so suddenly followed an infection, pelvic perivenous lymphangeitis might be the cause, and suggested exploration of the iliac vein. He had had the good fortune in America, in 1931, to hear Homans describing his original case, where decompression of the thickened lymphatic network around the femoro-iliac channel was followed by subsidence of the œdema within a few days.

Dr. PARKES WEBER said he thought the condition of the right lower limb was due to recurrent lymphangitic attacks following venous thrombosis at the groin. He would not advise any kind of operative intervention in this case.

Section of Epidemiology and State Medicine

President—J. A. H. Brincker, M.D.

[*November* 25, 1938]

Immunity in Influenza: The Bearing of Recent Research Work

By C. H. Andrewes, M.D.

Abstract.—The duration of immunity to influenza in man is difficult to assess from clinical data because of the difficulty of diagnosing the disease with certainty; two influenza-like attacks suffered by a patient within a short period may not have the same ætiology.

Serological relationships amongst strains of influenza virus are complicated. It seems probable that strains cannot be rigidly classified into types but that several antigens are present, distributed amongst strains in varying proportions.

The relationship of pandemic (1918–19) influenza to that of recent lesser epidemics is obscure. The supposed origin of swine-influenza in the U.S.A. in 1918 and the presence of antibodies to swine-influenza in the sera of most adult human beings have led to a suggestion that swine-influenza is a survival in the pig of 1918–'flu. The serological evidence for this view is now seen to be capable of other interpretations.

Factors concerned in the immunity of experimental animals to influenza are discussed—degrees of immunity in the ferret; immunity of the nasal passages to big doses of virus; immunity of the lungs; immunity to contact infection. Active immunity runs parallel with titre of neutralizing antibodies so long as one is dealing with one strain of virus. Cross-tests amongst different strains complicate the picture.

In planning vaccination of human beings we wonder:—

(1) Whether, on general epidemiological grounds, an attempt to vaccinate against influenza virus is likely to be profitable.

(2) Whether the production of a rise in antibodies in man will be a good guide to the immunity induced by a vaccine.

(3) Whether we are right in using killed virus and in fearing a live vaccine.

(4) What strains we ought to use in making a vaccine.

(5) When and how often we should vaccinate.

Résumé.—La durée de l'immunité contre la grippe est difficile à estimer d'après les donnée; cliniques à cause de la difficulté d'un diagnostic certain. Deux maladies ressemblant à la grippe chez un même malade à un court intervalle peuvent ne pas avoir la même étiologie.

Les relations sérologiques entre les souches du virus de la grippe sont compliquées. Il semble probable que les souches ne peuvent être classifiées rigidement en types, mais que plusieurs antigènes sont présents, distribués en proportions variées parmi les différentes souches.

La parenté de la grippe pandémique (1918–19) avec les épidémies récentes moins importantes est obscure. L'origine supposée de la grippe porcine en Amérique en 1918 et la présence d'anticorps contre la grippe porcine dans la plupart des sérums humains adultes ont mené à la suggestion que la grippe des porcs représente la survie chez le porc de la grippe de 1918. On comprend aujourd'hui que les évidences sérologiques supportant cette idée peuvent être interprétées autrement.

Les facteurs intéressés dans l'immunité des animaux expérimentaux à la grippe sont discutés : degrés d'immunité chez le furet, l'immunité des voies nasales envers de hautes doses de virus, l'immunité des poumons, et l'immunité à l'infection par le contact. L'immunité est parallèle au titre d'anticorps neutralisants tant qu'on s'occupe d'une seule souche de virus. Les épreuves de l'immunité croisé parmi les différentes souches rendent les résultats plus compliqués.

En considérant la vaccination humaine nous nous demandons :

(1) s'il est probable, d'après les principes épidémiologiques généraux, qu'un essai de vaccination contre le virus grippal soit utile ;

(2) si la production d'une augmentation du taux d'anticorps chez l'homme sera une bonne indication du degré d'immunité produit par un vaccin ;

(3) si nous avons raison d'employer un virus tué et de craindre un vaccin vivant ;

(4) quelles souches nous devons employer en préparant un vaccin ;

(5) quand et à quels intervalles il faut vacciner.

ZUSAMMENFASSUNG.—Die Dauer der Immunität bei der Influenza des Menschen ist auf Grund klinischer Daten deshalb schwer festzustellen, weil eine sichere Diagnosestellung nur schwer möglich ist : zwei influenza-ähnliche Erkrankungen, die ein Patient innerhalb eines kurzen Zeitraumes durchmacht, können eine verschiedene Aetiologie haben.

Die serologischen Beziehungen zwischen den verschiedenen Stämmen des Influenzavirus sind verwickelt. Wahrscheinlich können die Stämme nicht streng in verschiedene Typen eingeteilt werden, vielmehr scheinen mehrere Antigene vorhanden zu sein, die unter den verschiedenen Stämmen in verschiedenen Mengen verteilt sind.

Die Beziehungen zwischen der pandemischen Influenza 1918–19 und der kürzlich beobachteten weniger ausgedehnten Epidemien sind unklar. Der vermutungsweise angenommene Ursprung der Schweineinfluenza in den Vereinigten Staaten im Jahre 1918 und das Vorhandensein von Antikörpern gegen Schweineinfluenza im Serum der überwiegenden Mehrzahl von erwachsenen Menschen haben zu der Vermutung geführt, dass die Schweineinfluenza die im Schwein überlebende Form der Influenza des Jahres 1918 darstellt. Indessen weiss man jetzt, dass die serologischen Befunde auch in anderer Weise gedeutet werden können.

Es werden einige Faktoren besprochen, die bei der Immunität der experimentellen Tierinfluenza von Bedeutung sind : Immunitätsgrade beim Frettchen, Immunität der Nasengänge gegenüber grossen Virusdosen, Immunität der Lungen, Immunität gegen Kontaktinfektion. Die aktive Immunität geht mit dem Titer der neutralisierenden Antikörper parallel, solange es sich um denselben Virusstamm handelt. Kreuzweise Versuche mit verschiedenen Stämmen komplizieren das Bild.

Bei der geplanten Impfung des Menschen tauchen folgende Fragen auf :

(1) ob auf Grund allgemein-epidemiologischer Erwägungen der Versuch einer Impfung gegen Influenzavirus Aussicht auf Erfolg hat ;

(2) ob die Vermehrung der Antikörper beim Menschen einen guten Massstab zur Beurteilung der durch die Vaccine hervorgerufenen Immunität darstellt ;

(3) ob es richtig ist abgetötetes Virus zu verwenden und einen aus lebendem Virus bestehenden Impfstoff für gefährlich zu erachten ;

(4) welche Stämme zur Herstellung der Vaccine verwendet werden sollen ;

(5) wann und wie oft geimpft werden soll.

WE are all interested in influenza from one point of view or another ; it may therefore be of some value if I recount something of what is known of immunity to influenza in experimental ferrets and mice, and consider how far this knowledge is applicable in our attempts to understand the natural history of influenza in man and to guard against human infection.

On previous occasions summaries have been presented of the evidence for considering epidemic influenza as a disease due to a virus or closely related group of viruses (Andrewes, 1937). I do not propose to consider that evidence now, but to assume that influenza is a virus disease and to start out from that point. There is, however, a matter which cannot be so lightly dismissed : exactly what disease are we talking about ? Few would, I think, dispute that the name " influenza " covers

a variety of conditions, and unfortunately no one clinical criterion is yet available to help us to differentiate certainly between the virus disease and others resembling it. We have attempted the formidable task of trying to relate recovery of virus with a particular clinical picture. With this end in view my colleague, Dr. Stuart-Harris, with Drs. Chalmers and Cowen, has studied epidemics diagnosed as influenza occurring at schools or in the Services, and has sent garglings from patients to Hampstead to be tested in ferrets and mice by Dr. Wilson Smith and myself (Stuart-Harris, Andrewes, and Smith, 1938). The correlation of clinical and laboratory findings has shown that in years in which there is no major epidemic the minor outbreaks labelled influenza usually fail to yield a ferret-pathogenic virus. On the other hand, at epidemic times, as in early 1933 and 1937, it has been easy to recover virus from the large majority of garglings tested. We have provisionally considered the latter group as epidemic influenza and labelled the others " febrile catarrhs ", a name intended to be merely descriptive and not to imply a uniform ætiology. In other words, from the scrap-heap " influenza " we have removed an entity, identified it as " epidemic influenza " and then renamed the residue of the scrap-heap " febrile catarrhs ". While it is not yet easy to decide on clinical grounds to what group an isolated patient belongs, yet there are broad differences between the groups of patients in the virus-positive and virus-negative outbreaks so far studied. For instance, in epidemic influenza the onset is commonly abrupt ; in febrile catarrhs there are often premonitory catarrhal symptoms for some days before the patient has fever and has to go to bed. In epidemic influenza, in contrast to the other group, constitutional symptoms such as headache, malaise, and aching, predominate over catarrhal manifestations such as sore throat, coryza, and cough, particularly in the early stages. But of single cases it cannot yet be certainly stated on clinical grounds that this patient has or has not got epidemic influenza. During the 1936–37 epidemic two features, believed to be characteristic of " real 'flu " were absent from many patients from whom virus was actually recovered ; there was no regular tendency to protracted convalescence and so-called post-influenzal depression ; there was usually no leucopenia, most blood-counts taken in the acute stage being within normal limits.

I have gone into this matter at some length because I wish to emphasize that in endeavouring to find out how long the immunity of human beings to influenza lasts, one cannot place reliance on clinical reports that a given person had two attacks of influenza within, let us say, two months, or even on statements that a given institution passed through two outbreaks within a fairly short period. One may even be led astray by the occurrence of widespread outbreaks of something which looks like 'flu, yet isn't 'flu. Francis (1937) has described an epidemic diagnosed as influenza occurring in California in February and March 1936. Clinically and epidemiologically it resembled epidemic influenza much more closely than it did the febrile catarrhs just described ; in three towns there was an incidence of 30–40%. Yet he wholly failed either to recover influenza virus from the cases or to detect any rise of antibodies against influenza virus during convalescence. Another virus altogether, designated as the virus of acute meningo-pneumonitis, was recovered from ferrets inoculated with garglings from these cases. I say advisedly " recovered from the ferrets inoculated with the garglings " because Francis and Magill (1938) are themselves uncertain whether the virus undoubtedly came from the human material. It is at any rate possible that there is another virus which causes epidemics of an influenza-like disease in man, apart from the virus we have been studying.

It is also possible that different epidemics may be caused by serologically distinct races of influenza virus. It was thought at first that all human 'flu viruses were serologically identical, but as with foot-and-mouth disease virus, horse encephalomyelitis, poliomyelitis, and many other viruses, it now appears that serological varieties exist. If the ferret were still the only experimental animal known to be susceptible to influenza virus these differences would probably be still unrecognized.

Ferrets immune to one strain of influenza are immune, as a rule, to another, though immunity to homologous virus probably persists longer. Sera of a ferret recovered from any strain usually neutralize filtrates of any other strain. Quantitative differences in neutralizing power would be hard to demonstrate, for the ferret is too expensive an animal to use readily for elaborate quantitative titrations of sera. Mice, however, can be so used, and when sera began to be titrated quantitatively in mice, it became apparent that all human 'flu viruses were not serologically alike. Magill and Francis (1936) first demonstrated that this was so, using two strains of American origin, the PR8 and Philadelphia strains. In the last three years they have continued to worry at this problem ; so has Burnet in Australia, and so have we at Hampstead. The various laboratories have used rather different techniques, and the results obtained have not always been wholly concordant. Burnet (1937 *a*), for instance, has been growing viruses on the chorio-allantoic membranes of chick eggs and mainly studying the neutralizing power of sera in that way. Francis and Magill and ourselves have used neutralization tests in mice, but while the American workers have used immune rabbit sera and failed to obtain good results with immune ferret sera, our experience has been just the opposite. We recently agreed with them to publish our results simultaneously, and these have lately appeared in the *British Journal of Experimental Pathology* (Magill and Francis, 1938 ; Smith and Andrewes, 1938). In spite of differences in detail certain broad truths seem to emerge from the work of all the investigators.

First, there are undoubtedly serological differences amongst different human influenza viruses. Secondly, the viruses cannot readily be divided into types like pneumococci ; the various strains show more complicated overlapping relationships. We have tried to disentangle the confusion by selecting four strains which were much more specific and overlapped very little, and testing all other strains against these. We thus obtained evidence suggesting that four major antigens were represented in the different viruses, occurring in very different proportions. A few strains, our specific strains, were made up almost all of one antigen, with very little of the rest ; others (" master-strains ") contained all four in fairly equal proportions ; others (" intermediate strains ") were neither very specific nor very polyvalent.

Burnet (1937) attempted to divide the viruses serologically into Old World and New World strains ; this classification was all right for the strains then available to him, but most of those which have turned up recently in Europe have been more of the New World than of the Old World type. None of the strains yet isolated from America has, however, proved to be as highly specific as any of our specific types. Magill and Francis (1938) have, however, described minor differences amongst them, such as will allow hardly any two to be considered as identical. They are inclined to think that the viruses recovered from the 1936–37 epidemics in Europe and America are more closely related to each other than to strains obtained in previous years. We are disinclined to admit that much as regards English viruses ; the most widely differing strains appeared near London early in 1937, a most interesting point epidemiologically.

These serological races of influenza clearly have importance from two points of view. First, one wants to know about them in planning any experiments on active immunization against the natural disease. Our attempts to reduce the apparent chaos of different strains to order were directed largely to that end. Secondly, it will be of interest in the future, particularly in epidemics more limited than that of 1936–37, to see how far one serological race of virus is responsible for a given outbreak, to learn the epidemiological importance both of the major differences in strains which we have studied, and also of the more subtle distinctions amongst influenza viruses which Magill and Francis have been concerned with.

In particular we wonder what relation the virus of the 1918 influenza bears to the virus recovered from recent outbreaks. There is a natural tendency to think that

the disease was essentially the same as that caused by the virus we are discussing. Clinically they were alike except that severe pulmonary complications were far commoner in 1918.

Francis (1938) quotes American data which indicate that the first wave of the epidemic of 1918 afforded some protection against the second wave but not against the third, and neither of them against the 1920 epidemic. He thinks it possible that the third wave and the 1920 epidemic were due to an agent quite different from that of the first two 1918 waves; possibly one of the agents concerned was more closely related to that of the disease he studied in California in 1936.

It has been suggested in several quarters that swine influenza represents a survival in the pig of the 1918 type of epidemic 'flu. Apparently swine 'flu first appeared in the Middle West of America in August 1918 and has recurred annually ever since. Pigs are susceptible experimentally to human influenza, and Shope (1938) has obtained serological evidence that they may become spontaneously infected under field conditions; pigs fed on garbage at two institutions where influenza was prevalent were found a little later to have in their sera antibodies to the human but not the porcine strain of virus. It has been found that most adult human sera in England, America, and Australia, contain antibodies against swine influenza virus, while those of children born since about 1925 do not; the suggestion is obvious that the virus which stimulated their formation may have ceased to be prevalent since that year. However, this serological evidence has since been shown to be capable of other interpretations. Repeated inoculation of an animal with one strain of human virus broadens the zone of reactivity of its serum so that serum which at first is active particularly against the homologous virus, comes to react with other human viruses and even with the less closely related swine virus. A remarkable opportunity occurred for showing that the same was true of man. Search of the records revealed that St. Helena was the only place which certainly escaped the 1918 pandemic. Dr. Wilkinson, the Medical Officer, kindly sent us in 1935 sera from some of the inhabitants and these, to our great interest, mostly failed to neutralize swine 'flu virus as well as English sera did; for that matter they had but little antibody to human 'flu either. In the following year an outbreak of influenza occurred in St. Helena, and subsequent bleedings showed that most of the persons bled had sera with antibodies effective against both human *and* swine viruses. While we did not recover virus from this epidemic it seems likely that it was one of human influenza, and if so it appears that the porcine type of antibody can appear in man, as in experimental animals, as a result of infection with another type of virus (Stuart-Harris *et al.*, 1938). Burnet and Lush (1938) have adduced other serological evidence to favour this view. What we may call the "1918 'flu = swine 'flu" theory is thus deprived of any support from the serological studies of human sera. It is, however, not thereby disproved, only rendered more highly speculative.

In any event it seems a reasonable supposition, from what we know of biological instability of viruses in general and influenza virus in particular, that the 1918 'flu was due to a mutant or mutants of influenza virus. Such mutation may very well have affected first its antigenic structure—a change showing itself in the succession of waves of the disease—and secondly its affinity for the lungs. Two strains of the WS virus have been evolved in the laboratory, one capable of producing in ferrets a pneumonia which is often fatal, the other causing lesions only in the upper respiratory tract. A variant which especially attacked the lungs of man might associate itself with particular readiness with one or other of the pathogenic bacteria which caused such havoc in the epidemic twenty years ago.

I will now turn to some observations which concern closely attempts at active immunization of human beings.

In experimental animals immunity to influenza lasts for some months. It is a rough-and-ready rule that the smaller the animal the shorter tends to be the immunity,

so that we might expect on this basis that immunity to influenza in man would last for at least a year, perhaps more. There are, in ferrets, grades of immunity. For the first three months after infection there is what we may call Grade A immunity—proof against massive doses of virus given up the nose ; in Grade B, from three months onwards, the ferret is immune to the milder test of infection by contact, and, moreover, though he may take a nasal infection his lungs are still protected, so that even a highly lung-adapted strain of virus will not give him pneumonia. After a year or more he may sink to Grade C with no demonstrable immunity at all.

Influenza virus will only infect ferrets with certainty when given up the nose ; by subcutaneous and other routes the virus will commonly not infect. One can thus vaccinate with living virus given subcutaneously. Normal ferrets so vaccinated can be given a Grade B but only exceptionally a Grade A immunity ; that is, they can be protected against contact infection and against lung lesions, but not against massive intranasal doses of virus. Also, if one takes a ferret whose immunity after infection has waned from the A to the B level, subcutaneous vaccination will readily push it up to the A level again. Unfortunately we have failed, having given normal ferrets a Grade B immunity by vaccination, to push it up by further vaccination to the stage of complete resistance to the virus. Nevertheless, the ferret experiments are encouraging from several points of view to the would-be vaccinator of human beings.

(i) Man is not likely to be asked to withstand massive doses of virus up the nose. A Grade B immunity, effective against contact infection, may be good enough.

(ii) Even if we fail to protect wholly against infection, we may give so much immunity that, if another 1918-type of influenza occurs, we can protect the lungs by vaccination and so save many lives.

(iii) Most adult human beings have had influenza at one time or another and thus, like recovered ferrets, have some basic immunity. Vaccination may avail to push up this immunity from the B to the A level.

Before discussing further the possibilities of prophylactic vaccination in men I must make it clear that we are open to conviction as to whether active immunization is the right way to tackle the control of influenza. Are we convinced that a fall in the immunity level of the community is such an important factor in the causation of epidemics that an increase in that immunity level, supposing we can produce it, will prevent or modify an epidemic ? We have, of course, no grounds for such conviction. Nevertheless, the possibility of effective vaccination opens up an obvious and hopeful line of attack.

Epidemics come so infrequently, and strike so irregularly, that it is a most difficult task to test the value of human vaccination ; we have to vaccinate a community and then wait and see whether within a few months an epidemic strikes that community —a most exasperating and disappointing method of research. In hopes of getting some sort of guide as to the effect of vaccines in man, we have tested the rise in antibodies produced in them by vaccination. Thirty soldiers thus tested developed a most encouraging rise in antibody titre, averaging twenty-five-fold. We used formolized filtrates of infected mouse lungs and found that one dose of 2 c.c. produced as good a rise as did two doses spaced a fortnight apart. We tested the sera by examining their neutralizing activity for the same strain of virus (WS) as was used for the vaccination ; the increase against a serologically distinct strain was less, averaging only five-fold. Does this rise in antibodies mean increased active immunity ? Hoyle and Fairbrother (1937) have suggested that the titre of complement fixing antibodies may be a guide to susceptibility. The level of antibodies to the WS virus in the sera of man is, however, certainly not proven to be a guide to his susceptibility to attack during an epidemic. Smorodintseff *et al.* (1937) have reported that the success of an attempt at experimental infection of human volunteers with a passage strain of virus was closely related to the presence or absence in the sera of the volunteers of antibodies active against the same strain.

Here once more ferret experiments yield interesting information. In ferrets infected with the WS strain of virus there is good correlation between active immunity and the content of neutralizing antibodies in the serum. We have compared all sera with a standard immune horse-serum ; ferret sera five times as good as that standard usually accompany complete (Grade A) active immunity ; ferret sera better than one twenty-fifth of the standard usually imply at least a Grade B immunity. So far, so good ; but when we stop dealing with our WS strain and study swine influenza and other human influenza viruses it is a different story. Ferrets may be infected with swine influenza and with some of the serologically distinct strains of human influenza viruses ; on recovery they are usually immune to the WS strain although they may have few or no antibodies against it. Shope (1937) has found the same thing to be true of pigs recovered from swine influenza, and we have seen it also in mice. We therefore use antibody titrations as a guide in our human tests only because we have nothing else available.

The vaccines we have so far used on human beings have been treated with 1 : 5,000 formaldehyde, a procedure which can be relied upon to inactivate the virus. Such formolized vaccines will immunize ferrets and mice. We have thus played for safety in preferring to use a killed vaccine, although we know that killed vaccine is less effective than living, and that American workers have used living virus without ill-effects to vaccinate some hundreds of people. It must be remembered that virus used for vaccination will be introduced by the relatively safe subcutaneous route, and will also have been modified by animal passage ; much experience shows that repeated passage of influenza virus in the mouse renders it less virulent for the ferret and vice versa. Burnet (1937 *b*) has described a strain propagated on hen's eggs which readily kills the embryos of the inoculated eggs but is of very low pathogenicity for the ferret and mouse. He has inoculated this strain intranasally into man without producing disease ; no epidemic has yet occurred to prove whether persons so treated develop active immunity. In theory, this method of giving attenuated live virus intranasally might be expected to give a better immunity than would virus, alive or dead, introduced parenterally, for the virus in the respiratory tract would presumably multiply. It should therefore be possible to immunize more rapidly and with tiny doses of vaccine. But any reliance on the modification or attenuation of influenza virus by animal passage must at present be insecure ; a change taking place in one direction may, under appropriate conditions, be reversed. On the whole, since killed virus has been shown experimentally to produce immunity in animals, it seems worth giving it a trial in man before embarking on the more hazardous venture of using living viruses. At the same time it will be well to gain knowledge of how an attenuated virus might be employed, particularly to give rapid immunity in face of a dangerous killing epidemic.

The next in a succession of conundrums concerning vaccination are these : What source of virus should be used, and what strains of virus can best be included in a vaccine. The evidence available suggests that more virus can be obtained from mouse lungs than from ferret tissues or chicken tissue-cultures, though the last source would be far more convenient for large-scale manufacture of vaccine. So far, however, no evidence is to hand that inactivated tissue-culture vaccine is of any value for immunization. On theory, a polyvalent master-strain containing all the important antigens would be the one to choose for immunizing. Unfortunately our master-strains are all of low titre. In fact no strain except perhaps PR8 approaches the highly specific WS strain in titre, and so far as we can tell, this higher titre really reflects a greater quantity of virus in the lung emulsions of the mice infected with this strain. In a test now in progress we are using a vaccine made of a mixture of the high-titre monovalent WS and the rather lower-titre but relatively polyvalent PR8 ; this seems the best compromise to adopt for the time being.

Finally, when should one vaccinate ? Obviously a month or two before the next

epidemic is the time to choose. Since 1929 widespread epidemics in Britain have come at four-year intervals, but we hardly dare to hope that this regularity will be permanent, especially as other European countries have not experienced the same periodicity. At any rate, recent outbreaks have mostly begun in December or January ; so October and November are probably good months in which to vaccinate. One dose of vaccine brings up the antibody titre against the homologous virus very well, but it may prove that repeated doses are necessary to produce in man a broad immunological response with antibodies active against several strains.

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Section of Psychiatry

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Pre-Psychotic Anorexia

By Grace Nicolle, M.B., B.S.

The title of this paper is perhaps ambiguous, and in its very ambiguity lies its object. That object is to discuss the function of the diagnostic label as illustrated in certain diseased conditions characterized by anorexia. It is an attempt to display the twofold nature of this function as a security for essentials of therapy and a stimulus to a review of causation.

Pre-psychotic anorexia includes a range of cases, the most typical being "anorexia nervosa" which has in turn been assigned to the pure psychoneuroses or to the incipient psychoses. I shall describe a case labelled "anorexia nervosa" and pick out those characteristics which link it with allied conditions: such considerations may lead to deeper understanding and more fruitful treatment.

I select the case of Miss M. which I have been able to follow for some years and have had considerable opportunity to study. It corresponds in outline with the classical cases recorded by Sir William Gull and Charcot. The patient complained of nothing, but was brought for consultation by her parents, who were alarmed at her progressive loss of weight and her obstinate refusal to take adequate nourishment. The appearance of these cases is always arresting. My patient, Miss M., was then 19 years old; she was 5 ft. 6 in. in height and weighed 6 st. Her condition had begun insidiously, but had been fully developed for a year, with complete amenorrhœa. At this time she was 2 st. under normal weight and shrinking rapidly, though she had not reached such fantastic weights as 4 st., which are frequently achieved. She had by no means reached the terminal stage of exhaustion, and was still indulging in riding, tennis, walking, which produced so little fatigue that every interval was filled with feverish attention to self-imposed household tasks. The energy expended in this way was maintained on a diet which scrupulously excluded anything nourishing. She allowed herself grapefruit and a little toast, and at meals made a pretence of eating a scrap of meat with green vegetables. An obstinate constipation was the result of this starvation, and she cheerfully resorted to large doses of purgatives.

I ask you to imagine Miss M. as a skeleton decently but inadequately clothed in a meagre mantle of flesh, through which the bony prominences of every joint were clearly defined, as was the framework of limbs and thorax. The abdomen was concave and all swelling of the breasts had gone; the skinny neck looked unduly long and hardly capable of bearing the head, with its wizened deathly face and two dark burning eyes crowned by a tousled mop of glossy black hair. She was of mixed parentage; her father was a Greek and her mother Scotch, and from her father she inherited a typical modern Greek appearance and no small share of southern fire.

She had been fully informed that her cure in the nursing home would involve separation from her family, but she never believed that her mother would abandon her. When she heard her mother get into the car she rushed to the window and tried to throw herself out with hysterical screams which were luckily drowned by the noise of the engine ; she was left. From that moment she more or less gave in to be cured. Fortunately her parents were willing to acquiesce in a necessary isolation ; this resolution was forced on them by their inability to deal with the patient's mental attitude. This was peculiar : her natural shyness had become intensified and accompanied by scrupulosity and an unnatural solicitude for the welfare of others as long as she was left undisturbed in her regimen of exercise and starvation. Any interference with this immediately roused storms of remonstrance and actual violence, particularly against her mother.

After hearing the parents' account I felt the patient should be heard in her own defence, which was, however, totally unsatisfactory. She ascribed her behaviour to the most trivial causes. She says she is quite well, eats almost excessively and certainly could not eat more as she is not hungry ; she is not tired and exercise is essential if she is to eat at all ; everyone eats too much ; there is nothing the matter with her, it is all the stupidity of other people as she never felt better in her life. She gives a baffling impression of offended dignity which admirably masks a most obstinate determination. In the general management of this case the first essential of treatment is the restoration of nutrition, and all writers are agreed as to the methods, not always successful, which should be employed for the purpose. This " distemper " was mentioned by Morton as early as 1694 and again in 1789 by Naudeau, who graphically described " an amazing revulsion from food " ; but little attention was paid to it till the last half of the nineteenth century. In 1868 Sir William Gull drew attention to these cases, and in 1874 gave a full account of the successful treatment of several in the *Transactions of the Clinical Society*. Subsequently there have been many interested observers both here and abroad. There is general agreement on the two fundamentals of treatment ; the first is isolation and feeding under strict supervision, and the second is some form of psychotherapy. Isolation is essential in order to remove the patient from an environment which reacts emotionally to her condition and further to prevent interference of the parents in the treatment, for they cannot believe the consummate duplicity of their child, and if they do, ascribe it to moral perversion rather than mental disease. The patient protests with bland horror at the attendance of a special nurse and complains that no one trusts her and she will certainly eat all that is given her. But unless the nurse watches every mouthful disappear and remains beside the patient for a considerable time afterwards she will get rid of her food, down the water closet, the hand basin, or by concealment ; she lies unblushingly, and it is only a steady increase in weight which can give assurance that deception is circumvented. The patient should be put to bed to restrain insensate exertion, and will even then leap in and out of bed at the least excuse. She should be given food at regular intervals and in increasing quantity. What the patient should be given at first must be regulated by the individual condition. The attitude of the physician, whose inflexibility must match that of the patient, should combine a benevolent assumption of authority, " I know and you don't ", and a skilful evasion of all argument. This first stage is the most difficult, for the physician will be greeted by a recurrent demand for more liberty and less food, and though the patient apparently acquiesces, the sight of food is the signal for antagonism and tears.

The clinical manifestations of her state can be summarized under four heads :—

(1) Emaciation.

(2) Loss of appetite without digestive disturbance and reduction of food intake to a minimum.

(3) Persistent amenorrhœa.

(4) A peculiar mental state of a euphoric type.

With emaciation and loss of appetite the possibility of a wasting disease should be considered. Tuberculosis in particular must be considered as undoubtedly some of these cases die of it. In Miss M.'s case such a possibility was easily excluded. Apart from a pulse-rate of 44 and a systolic blood-pressure of 88 she showed only one other point of interest, and that was the growth of hair on the body. There was a general distribution of downy hair on body and cheeks, while the arms and legs were covered with coarse dark hair and lines of similar hair extended from pubes to umbilicus. In front of the ears, in what might be called the whisker region, the down was long and dark, and in general the hair grew close round the face. The growth of hair has been noticed by Ryle and others, and together with the amenorrhœa has suggested an endocrine disturbance. At this point comparison with another well-known wasting illness is suggested—that is Simmonds' cachexia. Since the original paper was published in 1914 the condition has been frequently described. Simmonds was first and foremost a pathological anatomist, and his observations are based on post-mortem findings of destructive changes in the pituitary gland, so that the clinical picture has been associated with observed organic change ; and it has been possible to institute cure by supplying the secretion which had failed through destruction of the gland. Careful observers have, however, recorded similar cases in which no organic change was found and in which a functional depletion of the gland must be accepted. It would be hard by superficial examination to distinguish in the middle stage between a case of Simmonds' disease and one of anorexia nervosa when certain later distinguishing features have not developed. The loss of appetite, the striking emaciation, and the amenorrhœa, are all comparable. There are, however, important differences in the evolution of the two conditions and in the mental attitude of the patients. The onset of Simmonds' disease is abrupt, that of anorexia nervosa is insidious ; in the former loss of weight precedes the reduction in alimentation ; in anorexia nervosa it is the result of the starvation. The amenorrhœa is usually a late event in Simmonds' disease, in anorexia nervosa it precedes or is coincident with the mental change which produces refusal to eat. The age-incidence in Simmonds' disease is more variable and less commonly associated with puberty ; it is confined to females and often occurs after circumstances which might induce pituitary exhaustion, such as pregnancy with hæmorrhage and prolonged labour. In the late stages of Simmonds' disease the teeth and hair fall out, a condition never noticed in anorexia. There is a profound difference in the patients' mental state. I have described the morbid energy and obstinacy of the anorexic, but these other patients show weakness, mental lethargy and somnolence, with a readiness to co-operate in treatment, though later delusions may make their appearance. I have consulted numerous authors in this connexion. Sheldon, Hawkinson, Herman, Schulmann, Loeper and Fau, Gennes and Delarue, and should like to make a few quotations from these sources :—

(1) That Simmonds himself thought that the cachexia was fundamentally mental in origin.

(2) Sheldon considers Simmonds' cachexia and anorexia nervosa are fundamentally the same except for predisposition in the latter.

(3) Here (in Simmonds' disease) the anorexia is a defence of the organism against food which it can no longer assimilate.

The long and interesting paper of de Gennes, Delarue and Rogé describes a typical case of hypophyseal cachexia with a fatal termination. An autopsy revealed no gross or microscopic change in the pituitary but complete atrophy of the ovaries and suprarenal cortex and some alteration of thyroid structure. Reciprocal relationships exist between these glands and the pituitary though we are far from understanding their precise nature, and these authors urge the use of the term Simmonds' syndrome to indicate the tentative state of our knowledge. In 1932 Baudouin, Lhermitte and Lérebouillet reported the case of a young man presenting the symptoms of Simmonds'

syndrome, where the autopsy revealed a tumour of the pineal. Endocrine disturbances can therefore be assigned as the cause of diseases which present strong affinities with anorexia nervosa. The endocrine basis of this latter is " unproven " but has been frequently adduced. Léopold Lévi and others regard it as due to thyroid deficiency and point to the slow pulse and low basal metabolic rate ; but the cases described are not typical and on the whole thyroid has fallen into disuse.

Many observers are, however, satisfied that the whole pathology of anorexia nervosa is the pathology of a condition of starvation. I quote from Ryle's masterly article in 1936 : " It may be doubted if anorexia nervosa possesses a morbid anatomy, histology or chemistry of its own if we except those changes which come about as the result of starvation and a depression of the menstrual function." He, however, emphasizes the amenorrhœa and the hirsuties and says of the former " it accompanies the disease from the beginning and is an expression of the initial nervous trauma which accompanies the malady from inception to cure ". He suspends judgment on their significance. In May of this year a paper was published by Wallace Ross in the *Lancet* directed to proving that the pituitary gland has no relationship to this condition. It is easy to agree that the disturbances of carbohydrate metabolism on which he bases his argument can be fully explained as the result of starvation alone without any theory of glandular deficiency. The case which he quotes does not suggest the mental picture of anorexia nervosa, and as she was a girl before the onset of the menses his arguments are deficient in one vital particular. He summarily disposes of the significance of amenorrhœa in these words : " In all probability therefore amenorrhœa can arise either directly or as a consequence of wasting, independently of any special endocrine disorder." This was certainly the earliest supposition with regard to this feature of the malady, but later observers are almost unanimous in saying that many cases show an obstinate amenorrhœa which persists long after appetite is restored. A French writer, Ballet, states : " As long as the patient has amenorrhœa she is not cured. Even if she has become plump, relapses must be feared as long as the menses are not restored."

I should like to illustrate this point in the case of Miss M. She remained in the nursing home from August 1932 to the end of April 1933. During this time she put on 1 st. 10 lb. in weight ; she looked blooming and was living a normal life without special supervision. The tendency to compulsive exercise was gone and she had become much less seclusive. The menses had not reappeared since her last period in August 1931. After a short visit home she went to live in a family at one of the Universities to prepare for the entrance examination, as she wanted to study literature. At that time I had tried various pituitary and ovarian preparations with no success, and her mental condition still appeared unstable. In August 1934 I gave the patient a series of injections of progynon and proluton following Kauffmann's technique, and at the end of four weeks there were menstrual pains. A second series of dimenformon and progestin was followed by a period, the first she had had for three years. An immediate change for the better took place in her mental outlook and she expressed a joyful feeling of being a normal girl. I must not, however, minimise the fact that at this point she passed her entrance examination, no mean feat for a girl who had never had any proper schooling.

The mental state of these patients is of foremost interest, and it would be impossible to discuss it without facing the question of motive. I shall here tacitly assume that we accept Freud's theory of the Unconscious and all his major affirmations but permit ourselves to question their universal validity.

The refusal to eat is no uncommon symptom in mental disease, and it is necessary to attempt some differentiation. Melancholics frequently refuse food, but their refusal can always be directly referred to their delusions of unworthiness. Patients in states of elation may exhaust themselves by neglecting their meals, but this is rather a result of the flight of ideas which carries them away heedless of consequences ; the

norexic has no flight of ideas but rather a fanatical domination by one idea. Again patients suffering with paranoia will refuse their food, due to ideas that they are being poisoned. Anorexia nervosa was at first regarded as a form of hysteria or possibly hypochondria, but this was displaced in favour of a more serious classification as dementia præcox. The refusal to eat would then be regarded as part of a characteristic negativism. It may be noted that Robert Dubois in 1913 published an account of a case which began as a typical anorexia nervosa and in ten years' time was a fully developed schizophrenia. Several French authors describe a type of case which evolves from hypochondriacal ideas about the digestive function, fostered by the institution of diets and leading finally to loss of appetite and refusal of food ; they may well be variants in a long series of allied conditions.

The differentiation between hysteria and anorexia nervosa is of the first importance as it must largely govern our selection of treatment. At the present moment I have two patients, one with anorexia nervosa and the other with hysterical abstention from food. The first has run a very chronic course with long periods of amenorrhœa and no other symptoms. The second has always had regular periods, her breasts are normally developed, though the rest of her body is much reduced by starvation ; she further presents alternatively attacks of asthma and urticaria. A mono-symptomatic hysteria is a doubtful candidate for classification with that protean disease. The superficial mental attitude of the two patients is sharply contrasted. The hysteric makes parade of her inability to eat and undoubtedly eats when it suits her ; the anorexic tries to dissimulate the fact that she does not eat. The hysteric desires to elicit sympathy ; this is far from the anorexic, but she may enjoy in some less direct way her ability to tease and deceive those about her. I should say that the purpose of the anorexic to starve herself is of fundamental importance. This is illustrated by their different reactions to isolation : emotional neutrality in the environment will make the hysteric eat in order to escape to one more congenial to her purposes, and we know she will eat when unobserved. Not so with the anorexic, who will only eat when under strict supervision. The hysteric welcomes attention from her environment directed to her disabilities, while the anorexic is mysterious and tries to evade inquiries ; it is as though the hysteric plays a drama to her environment and the anorexic to herself. An analytical investigation in the case of this hysterical patient has produced a perfectly coherent picture of psychological causation. Her age is 32, old for anorexia. She was the eldest daughter of a marriage seemingly devoid of all emotional significance ; the wife had money and land and the husband managed it. They belonged to an almost extinct race of minor landed gentry and both were devoid of emotion and imagination. The mother only wanted a son to inherit her property and had no use for two elder daughters, merely showing vague signs of life when a son was born nine years after my patient. This child knew no tenderness or love from the mother, whose stupidity inflicted constant minor cruelties ; she had no emotional rapport, no security. Her constitution was allergic and she soon discovered that her attacks of asthma were the only thing that roused her mother's attention. Her asthma lasted till adult life and disappeared during psychological treatment. In spite of her unfavourable surroundings she had a good deal of spirit, and after much opposition she escaped from home and qualified as a radiographer. Alas, having so escaped, she did not find herself capable of securing in the world the valuation she so sorely needed, nor was her work able to contribute much emotional satisfaction. She therefore never applied herself seriously to her profession, but fluctuated between work and home lest they forget her entirely. At home she obtained some satisfaction by causing anxiety about her asthma and the dangerous nature of her work. Presently her mother died, and then she transferred her operations to her father, who failed entirely to be moved by asthma. A new symptom was clearly needed, and at this point she began to starve herself. This proved efficacious and roused her father's attention by a curious echo from infancy. She had been difficult to feed ; her mother

could not do it, and no satisfactory substitute could be found till, faced with the loss of his child, the father enlisted the services of a donkey, on whose milk this unhappy child survived. Frustrated and unhappy in later life, she wished to bring about the death from which she had been saved and by a method calculated to wring the hearts of the most stony parents. She stated her difficulty thus : " If only I were happy I could eat and be fat and how I long to be fat for that would mean I was happy." In spite of a great reduction in weight there was no loss of appetite in the strict sense. Many authorities on anorexia emphasize that the refusal to eat brings with it a loss of appetite which is physiological.

We can appreciate hunger and appetite as two conscious elements in physiological sequences. Hunger is awareness of the general need of the organism for fresh supplies of metabolic material, while appetite is the knowledge of the presence of, or memory of, suitable substances to meet the need. These two combined result in action—the ingestion of food. The thesis of Noguès, *Anorexie Mentale*, passes in review numerous theories of the physiology of hunger and the balance of evidence minimizes the rôle of gastric contractions as a primary cause of hunger ; these localized sensations are rather an echo of a general cry for restoration. The arguments excellently presented in Wallace Ross' paper, which seek to explain anorexia nervosa on a basis of the physiology of starvation, appear too dogmatic. No doubt fluctuations in blood-sugar level are part of the mechanism by which we recognize our bodily needs, but we are still in the dark as to influences which may affect these signals. The condition of cellular metabolism must be fundamental, and this is intimately associated with the activity of thyroid and ovaries and influenced by the circulation of toxins. Perhaps we may say that in true anorexia nervosa the loss of the sensation of hunger may be due to glandular interference with cellular metabolism, but that its real importance is that it enables the patient to pursue her morbid purpose without undue distress, rather than acting as a cause for perpetuating the fast. What then is this morbid purpose ? In all cases I have seen, behind the trivial excuses offered lurks a fanatical desire to be thin and a dread of obesity. Miss M. said : " I am terrified of getting fatter or even of not getting thinner." The psycho-analytic interpretation of this state of mind would regard fatness as the sign of indulgence in the pleasures of the mouth and that the intense guilt associated with these impulses must be penalized by starvation and purgation. Such mechanisms can be brought to light in analytic investigation of these patients, but their restoration to consciousness does not seem to produce an amelioration of the condition as in other compulsive states. They appear to exist apart and not to be charged with the profound affect latent in this condition. Obesity appears to be dreaded rather as an unbearable affront to narcissism. Perhaps we can more fruitfully inquire into the circumstances attendant on the inception of the malady. One writer puts it thus : " the soil in which anorexia nervosa grows is adolescence." What is this " soil " of adolescence ? We know its physiological instability and something of its psychological difficulties. It is to these latter I would first draw attention, and I should like to quote a passage which I recently encountered in a French novel, for in many ways the French have the most penetrating insight into feminine psychology. " The only satisfactory destiny for a woman is a happy marriage. Thus she is dependent on a man and she knows it very early. It is true that an adolescent boy suffers from feelings of impotence and inferiority, but he knows that the young man he will be by and by can do what he likes with his future. A girl fears the future. A boy knows his future will be what he wishes, while a girl knows that hers will be what a man wishes. During this period of adolescent uncertainty a girl is more prone to daydreams of happiness because in advance the achievement of that happiness is uncertain." Stated more crudely—adolescent anxiety in a girl centres round doubts as to her ability to influence her environment to secure a mate. When an anorexic patient begins to confide her troubles they are always associated with doubts of sexual

potency. She does not have periods like other girls, she does not experience the sexual thrills that others describe, she feels unable to attract boys. The majority of cases are to be found among the leisured or wealthy classes and among girls who have been spoiled and petted. Marriage is usually the only possibility visualized in their education, the only means of self-realization, the only claim recognized. Spoiling is the fostering of narcissism. Miss M., brought up abroad in the luxury of a white society employing native servants, was a little princess, and she expected a fairy-tale success. What are the likely reactions of a girl so nurtured when faced with a vaguely perceived inability to fulfil her sexual rôle? The situation will generate anxiety as surely as the threat of war to a community. There are not lacking other factors which stimulate her fears. Mothers with their eyes on the marriage market show anxiety about the amenorrhœa and are not always guarded in their comments. Miss M. said to me: "I did not worry much about my periods till mother said, 'I couldn't let anyone marry you unless that comes right'; I knew I didn't have the same sex feelings as other girls, I began to think I was a freak." The anorexic associates the plumpness of adolescence with her sense of sexual insufficiency and begins to try to remedy this obvious sign by dealing drastically with the fat. As soon as this mechanism is set in motion many secondary motives make their appearance and satisfactions are obtained by the revival of infantile partial sexual elements and by the mystification and annoyance of her parents. I have had opportunities for making prolonged attempts at analysis with these patients and have never been able to satisfy myself of a causal psychological sequence such as there is in my case of hysterical anorexia. The material appears in a much more disjointed way, not bearing an adequate emotional relation to the picture, much as material is produced in certain schizophrenic cases. Paraphrenics and paranoid schizophrenics show discharges of affect connected with their delusional systems which are comparable in quality with the discharges encountered when we interfere with an anorexic. The hatred and aggression thus roused are not adequately discharged through a parent transference, as in the case of a hysteric, but remain as it were a primitive rage, the result of affronted narcissism.

I have just read a lucid and illuminating article by Mayer-Gross on the early diagnosis of schizophrenia, and I should like to quote a few lines from it:—

"The normal emotions of affection and sympathy for the patient's nearest relatives and friends cool off or take on a quality of shallowness during a commencing illness. More primitive emotional reactions—for example fear or rage—are preserved longer."

This corresponds closely with the affective state in anorexia nervosa. Should we therefore think of this condition as a latent form of dementia præcox? It may well be as in the case of Dubois. Miss M.'s mental processes show a distinct schizoid tendency. In her finals at the University she received much credit for an essay savouring of mad genius; in an endeavour to present the cosmic implications of tragedy she soared away into the nebulous realms of modern physics and treated the fourth dimension with a familiarity Einstein might envy.

I believe that psychological treatment helped Miss M. by giving her more insight and developing less barbarous values, but I do not think she is stable, and I have been able to watch fluctuations of her mental condition closely following the state of her menstrual function. This has never been completely established, and at times she still requires ovarian hormones, to which she responds mentally and physically.

Earlier in this paper my perforce sketchy references to Simmonds' syndrome may have appeared to obscure rather than illuminate, but I hope that I have now clarified my line of thought. It leads me to the conclusion that anorexia nervosa is connected with primary ovarian failure as Simmonds' cachexia is with primary pituitary failure, the interrelationships of these glands allowing many variations of the essential picture. Noguès in 1913 suggested the likelihood of ovarian failure, though at that time adequate substitutes were not available; in 1937 Vidart published an admirably thoughtful article on mental anorexia and indicated ovarian therapy as one of the

essentials of treatment. We do not know the relationship of ovary and pituitary to tissue metabolism, but I have noticed that when an anorexic regains normal weight she does not attain a graceful, attractive figure, but shows a tendency to puffy lumpiness. This might suggest thyroid deficiency but is unaffected by exhibition of the extract. Can we venture to postulate a faulty state of tissue metabolism which interferes with the normal signals governing the sensation of hunger and is due to the lack of essential hormones ?

If therefore anorexia nervosa has its springs in the instability of the sex glands in adolescence, it would be reasonable to think that milder cases indicate only a functional retardation of development. The school and home environments may make too great physical and mental demands on these patients ; rest and re-alimentation in a neutral setting may allow spontaneous establishment of the menstrual function. More severe cases would indicate some constitutional factor of inherent gonad deficiency. The male cases reported appear to be of a severe type. Fatness is not a phase of development in boys as it is in girls at adolescence ; the fat boy at this age is therefore more likely to be a glandular dyscrasia than the fat girl. A fear of fatness in a boy leading to self-starvation is therefore likely to be associated with profound gonad deficiency and to prove resistant to treatment.

It would be satisfactory to be able to place the abnormal hairiness of these patients in coherent relationship with the picture they present : this I cannot do. In the case of Miss M. there was a general distribution of downy hair and also coarse dark hair on the limbs, linea alba, and in front of the ears. The general distribution of downy hair is most commonly seen, and it tends to disappear when the patient is well. I have never seen any development of beard or moustache in these patients, as is common in schizophrenics and in women at the menopause. They do not present the anomalies of hair distribution recently described in association with a pathological state of the adrenal cortex. I do not know whether such hairiness is found in famine victims ; it is certainly absent in the case of hysterical anorexia I mentioned, but it is seen in some cases of tuberculosis. It does not seem to indicate masculinization but rather a degeneracy or animalization.

My endeavour has been to show anorexia nervosa as a recognizable high-light in a series of varied conditions associated on the one hand with dementia præcox and on the other with definite endocrine disorder. Such a survey leaves everything in doubt, but this is a paper for discussion, and if it opens fruitful lines of thought its title and its purpose will be justified.

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Discussion.—Dr. NEILL HOBHOUSE : I was very much interested by Dr. Nicolle's review of the various factors—neurotic, psychotic, and endocrine—which at different times have been held to underlie this disorder. Many of us who have seen these cases during a number of years have oscillated to some extent between them. We did not find it easy to explain them as purely neurotic ; mainly because they were inclined to die. Then the idea of a schizophrenic origin presented itself as a refuge from these difficulties. I was driven from this refuge when I first read Dr. Ross' " Enquiry into Prognosis ". Dr. Nicolle finds difficulty in accepting a mono-symptomatic hysteria ; it seems to me that a mono-symptomatic schizophrenia with a recovery-rate of 80% is an idea still harder to assimilate. Then in recent years the idea of an endocrine basis came into prominence, and was strongly reinforced by the clinical resemblance between anorexia nervosa and Simmonds' cachexia.

I think it is beyond doubt that a condition of true pituitary cachexia exists, which includes the type of case described by Simmonds and also many which run a much more benign course, and some of which respond to treatment by pituitary extracts. But I am firmly convinced that this disorder differs fundamentally from the type of case which Dr. Nicolle has described to-night, and I do not believe that there is any valid evidence for attributing the latter to pituitary defect. I have observed some cases which were regarded by me and others as pituitary cachexia, and I very much doubt whether a real anorexia was an essential symptom. I remember particularly one case, a girl aged 19 with prolonged amenorrhœa and emaciation ; she was a poor eater, but to talk of anorexia would be exaggeration. She was perfectly co-operative, and there was no difficulty in getting her to take a diet containing full calorie requirements, and on this entirely adequate diet she continued to lose weight. I believe that, whereas in anorexia nervosa the wasting is the direct result of starvation, in Simmonds' disease this is not so ; they may lose weight on an adequate diet just as does the thyrotoxic.

In a disorder such as anorexia nervosa where pathological evidence is lacking, but clinical features are remarkably constant, insight into its nature must best be obtained by a close evaluation of the latter. One of these features, though it is fully recognized, seems to call for more explanation. If one considers the diets which these patients have usually been consuming before treatment it is not only the quantity which is abnormal ; they have a way of selecting a remarkable mixture of meat extractives and carbohydrate slops. The effect of feeding a normal individual on this diet would be twofold ; it would lead to emaciation and it would cause dyspeptic pain. This is just what does not happen in anorexia nervosa ; even though the alimentary condition is complicated by obstinate constipation which is dealt with by drastic purges no pain is experienced. Sufferers from this disease do not feel the sensations of appetite, or the pangs of hunger, or the dyspeptic pain which would normally be evoked by the existing conditions. In this complete unawareness of the sensations connected with nutrition I am reminded most of children suffering from pink disease, where there is undoubtedly a blocking of autonomic impulses by physical

disease. In anorexia nervosa it seems obvious that there is a disturbance of function somewhere in the endocrine-autonomic system, but are there any grounds for locating it in the pituitary? Surely there is a block in the *afferent* impulses from the viscera, in the autonomic nerves, and these patients suffer from an anæsthesia and analgesia resulting from it.

When the disease progresses unfavourably the clinical picture passes on to one of starvation. But I am not sure that the picture is quite that of starvation from other causes. I have never observed in patients or in records the appearance of œdema, or the development of ketosis with its resulting symptoms. It is possible that even in starvation the autonomic system of these patients does not function in the customary manner.

As to the nature of this blocking of afferent impulses, all the evidence available is against the presence of any physical disease. It seems therefore most likely that it is of the nature of dissociation, which brings the pathogenesis into the category of hysteria. I know that this view will be unacceptable to many psychiatrists, Dr. Nicolle among them, and I would like to put forward some considerations in defence of it. Dr. Nicolle discussed with great acumen the differential diagnosis of anorexia nervosa and manifest hysteria, and her remarks certainly carried conviction. But I would suggest that anorexia nervosa is of the nature of *conversion-hysteria*, which often does differ in much the same way from the more usual forms, and simply consists of a dissociation of certain neurones of a distribution corresponding with an idea. Those conversion-hysterias which we see rather little of now, but which we saw much of in the War, were quite often mono-symptomatic—at any rate until someone "cured" the symptom; then they sometimes became poly-symptomatic. My own belief therefore is that anorexia nervosa is primarily of psychogenic origin; that the patient becomes protected from the discomforts and pains of starvation by dissociation of afferent neurones, and that the ensuing bodily changes are purely secondary to inanition.

It seems to me that the idea of a primary ovarian failure, to which Dr. Nicolle inclines, must for the present remain in the balance. Ryle commented on it as follows: "The occurrence of the disease in males and in women after the menopause reminds us that a primary ovarian dysfunction cannot very well be claimed as an essential cause of the disease." Unless we find grounds for believing that the cases described in males were something different from anorexia nervosa, I do not see how the validity of this statement can be disputed. I certainly think that one of the ways in which the elucidation of the pathogenesis of anorexia can best be served in the future will be by a critical investigation of any cases which may be observed in men.

The PRESIDENT, after congratulating Dr. Nicolle on her admirable paper, referred to cases of anorexia in which the main factor is a refusal to accept destiny. He referred to the speaker's quotation from the French novelist, in which it was suggested that the greater frequency of anorexia in females as compared with males was attributable to the fact that the girl cannot look forward to shaping her own destiny in the same way that the youth can. In this connexion he described a case of acute anorexia in an undergraduate aged 20, who had adopted starvation as a compromise form of suicide and as a protest against a destiny which biologically and functionally was completely unacceptable to him.

Dr. W. PATERSON BROWN: Dr. Nicolle has shown us the fear of sexual inadequacy in the anorexia nervosa patient. She has related the not eating to a fear of growing fat, and consequently sexually unattractive to the male.

This explanation is superficial and inadequate as it does not recognize the active repudiation of sexuality which is going on in these cases and which I should like to stress.

At the deeper and more primitive level of the mind where this occurs the ingestion of food symbolizes impregnation and obesity pregnancy.

In this connexion it is interesting to reflect on those mental hospital patients for whom tube feeding has become a conscious sexual experience.

I have myself come across two such cases while working at a mental hospital.

Section of Urology

President—H. P. WINSBURY-WHITE, F.R.C.S.

[*October* 27, 1938]

Some Interesting Features Concerning 455 Personal Cases of Urinary Calculus

PRESIDENT'S ADDRESS

By H. P. WINSBURY-WHITE, F.R.C.S.

WHEN we consider urinary calculus as it occurs amongst us to-day we are struck with the different form which this disease takes compared with the reports of the incidence of it up to half a century ago. For until that time this complaint was mostly found in the form of vesical calculus in children of the working classes. When we realize that this type of case is practically non-existent in Great Britain at the present time, we find ourselves with some interesting material upon which to reflect.

The revolution has been a slow one and has gone hand in hand with the improving standard of living in the lower strata of the people.

It has fallen to the lot of research workers in the past thirty years gradually to fit together the successive pieces of evidence which have made it abundantly clear that the fault was one of diet. One may say that diet has always been a matter for great consideration in connexion with attempts to reduce the recurrence of calculus. The old conception, however, that the presence of stone depended largely on the ingestion of the chemical substances of which the stone is composed, has now almost faded into insignificance.

When the incidence of stone has a relationship to diet, it is to do with deficiency, rather than excess, of food constituents. Deficiency of vitamin A of animal origin has been proved to be an important fault, while another factor has been shown to be some unidentified constituent of the whole meal of cereals when taken under certain conditions. It is from the work of McCarrison in India that so much proof on these matters has been forthcoming. Butter and milk, and wheat milled under modern conditions, have been the safeguard in our times against vesical calculus in children.

With regard to the incidence of stone my own cases accord roughly with those of many others. The principal features of such an analysis are as follows: Stone is twice as common in men as in women (males 294, females 161); about 78·4% occurs in the upper urinary tract. Renal calculus is somewhat more common in the male (male 128, females 108). In the ureter this preponderance is very definitely established, for here calculus is twice as common in the male as in the female. Another interesting fact is that the disease is more common in the left kidney than the right (left 109, right 86, bilateral 41), and that when we come to the ureter this discrimination is even more marked still, my figures being: Left 70, right 47, bilateral 4. The average age for stone in the upper urinary tract is 39·6 years.

Seeing that the maximum incidence of this disease in the upper urinary tract is towards the end of the fourth decade of life, and that the cases due to proved dietary errors occur largely in the lower urinary tract in children, there must be an ætiological factor other than any of those already proved to explain our present-day cases. There are certainly a number of constitutional disturbances which encourage lithiasis; but it is difficult to explain the great bulk of the cases in this way.

The astonishing stone wave of central Europe which apparently started about 1924 and still continues, most likely expresses a widespread change in the conditions of life in those parts, but what those essential factors are has yet to be discovered. That the fault is dietetic is highly probable, and that it is different from those errors which have already been identified is equally likely because the form of the disease has altered in that it is renal instead of vesical, and it occurs in the middle-aged instead of in children.

I have been very much impressed with the fact that a high proportion of renal stones have been associated with identifiable chronic lesions indicating a past or present inflammatory change of the genital organs, the urethra, and the bladder-neck. Often these have not been very obvious, and in many cases would certainly have been missed if they had not been sought for carefully. In some cases, and I am speaking of those before middle age and of females as well as males, residual urine was found to be present in the bladder. This seems to be due to some bladder-neck change which in its turn may in some cases be the result of a past inflammation.

In 115 cases of stone in the upper urinary tract I have found either a focus of infection in one of the situations mentioned, or there has been residual urine in the bladder, in as many as 72%. It is surprising how often residual urine is found in the bladder, and the epididymes are thickened if not actually adherent to the testes, with some recognizable change of the internal genitals on palpation ; although occasionally endoscopy will be necessary to establish the presence of inflammatory changes in these organs.

It might be thought from what I have said that gonorrhœa should be commonly associated with stone. This is not the case, but the mixed infection which lingers indefinitely after this infection, in time undoubtedly plays its part, as many of my cases have shown ; others have emphasized these points. Cervical erosion is quite a common association, and so are chronic urethral and prostatic infections.

Now I would like to describe early pathological changes in a kidney, which is a stone-forming organ. Randall of Philadelphia has described how stones form on the renal papilla, first of all under the epithelium as a minute plate of calcium, on which other crystals are deposited ; thus a tiny stone develops which breaks away, carrying a facet or depression representing its point of attachment to the papilla.

It is obvious that a stone bearing such characters must be extremely small, as, after resting in any part of the urinary passages for any length of time, it will soon become coated with further crystals, and thus the evidence of any papillary attachment is inevitably buried.

I have been fortunate in being able to collect five very small calculi which show these facets ; each stone was passed by a different patient following an attack of renal colic. The physical characters of these stones invite the conclusion that there is an area on the surface of each which represents its former point of attachment to a papilla. The diameters of these stones vary between 2·5 and 4·5 mm. I have examined them all microscopically under a 50-mm. lens with direct light illumination, and their important characteristics are portrayed in this drawing (fig. 1). Dr. J. Fine, the pathologist at St. Paul's Hospital has analysed these stones for me, and he finds that they all consist of a mixture of calcium oxalate and calcium phosphate with a trace of carbonate and organic matter.

An additional stone larger than the others, actually 7 mm. in its longest diameter, is depicted separately. The appearance of this stone, two views of which are presented, suggests that following its detachment it has become completely covered with a further deposit of crystals, but that the zone of attachment (a depression) is still apparent (fig. 2).

There is no doubt that stones form in the kidney in localities other than the papillæ. Here, for example, is a drawing of a kidney where calculi are firmly adherent to ulcerated areas of the pelvic mucosa (fig. 3).

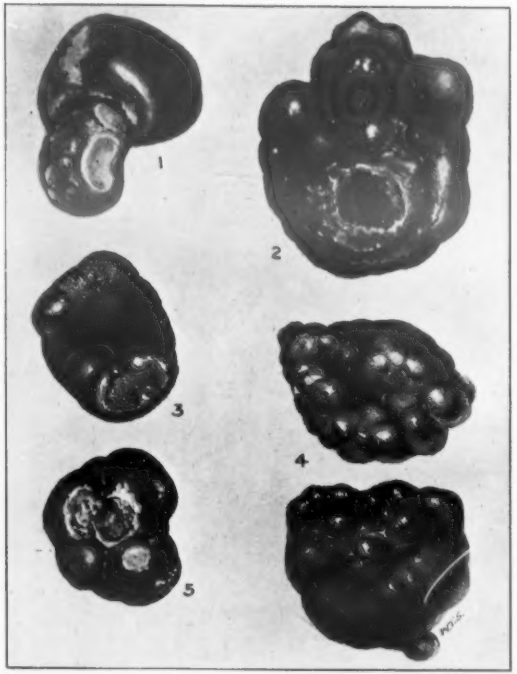

FIG. 1.—A collection of five small stones, each passed by a different patient after an attack of renal colic. Each calculus shows a facet or a depression which probably represents its point of attachment to a renal papilla. No. 4 represents two aspects of the same stone.

FIG. 2.—Larger calculus with a depression. Size and appearance probably due to further deposition of crystals since detachment from papilla.

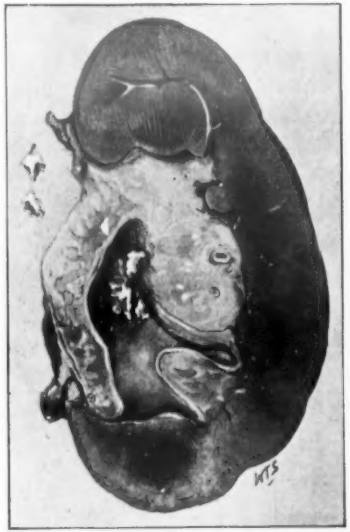

FIG. 3.—Calculi formed on patches of ulcerated pelvic mucosa.

The depth of fat surrounding the pelvis indicates the chronic nature of the pyelitis which was present. The patient had, over a course of many months, passed a number of stones.

Here are some drawings of a kidney showing that renal calculi can form under rare conditions (fig. 4).

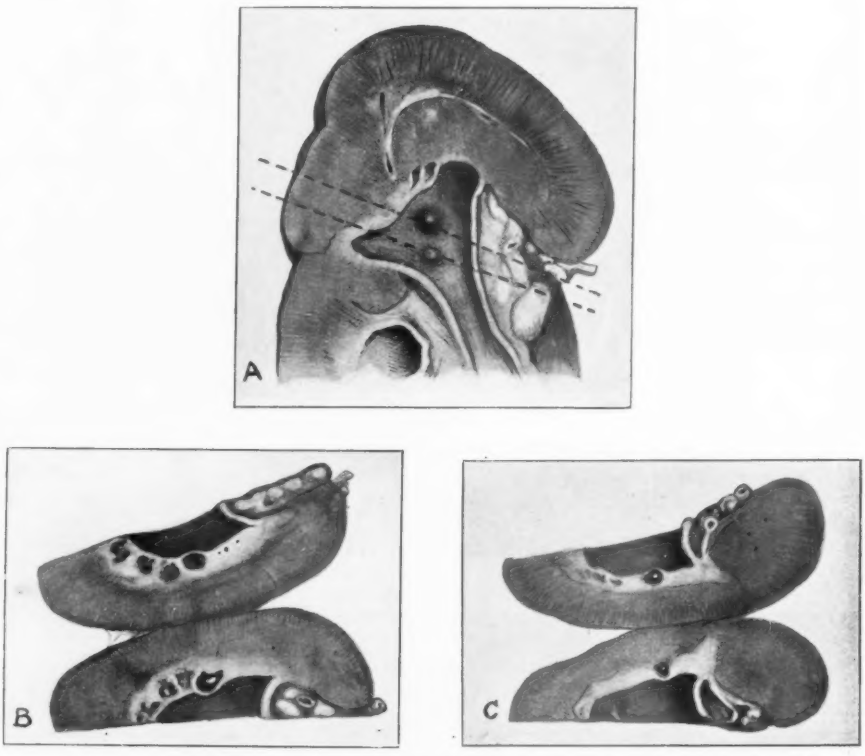

FIG. 4.—Calculi formed in closed cavities beneath the mucous membrane of a renal calyx.

They have developed beneath the mucous membrane in closed cavities which have apparently formed by the breaking down of renal substance.

Calculi may occur in more than one part of the urinary tract at a time. The following table shows the different situations of the calculi when these were multiple in 455 cases of urinary, and 29 cases of prostatic calculi :—

Situation	No. of cases
Bilateral, renal	41
Bilateral, ureter	4
Kidney and ureter	24
Bladder and upper urinary tract	2
Bladder and urethra	2
Urethra and elsewhere in urinary tract, or prostate	5
Prostate and some part of urinary tract	5

Changes in the kidney.—I have long since felt convinced that one of the important ætiological factors in the formation of renal calculus is an already existing dilatation of the pelvis, often only in a minor degree, but nevertheless capable of producing a certain amount of urinary stasis. Intravenous urography has given us the means of identifying many cases of this kind. The most convincing examples in relation to stone occur where the dilatation can be seen on both sides, while the calculus is present only on one side (fig. 5).

Single or multiple rounded calculi seen in the renal area of a radiogram are those which have formed secondarily to a hydronephrosis. I have discovered this association in about 10% of my cases. It is particularly marked in children ; in fact in the majority of cases of stone in the upper urinary tract in children there was previous hydronephrosis (80% of my cases) (figs. 6 and 7).

Clinical features.—Diagnosis by X-rays as a rule does not present any difficulty, but there are the odd cases where the appearances raise a doubt. Where any uncertainty exists it is generally a question of calcareous glands. On a lateral radiogram gland shadows are almost invariably seen well in front of the vertebral bodies, whereas the shadows of renal calculi are usually confluent with those of the vertebral bodies. Exceptions to the latter rule are found, however, from time to time (fig. 8).

I avoid instrumental pyelograms in renal stone cases because of the danger of stirring up infection in the kidney. The less dense shadow from the excretion pyelogram is so much more satisfactory as a means of showing the exact position of the stone in the kidney ; and I never fail to make use of this method, for in addition, it gives so much information about both kidneys without any risk to the patient. And, as a rule, by this means one is able to make up one's mind before operation exactly what operative treatment should be carried out.

It is not often that calcified tuberculous masses in the kidney raise a doubt with regard to stone, but I had two cases which deceived me in this respect (fig. 9). Then there is also a condition which sometimes occurs in the kidney as a solitary circumscribed mass giving a shadow on X-rays. The substance is yellowish, semi-solid, and homogeneous. I had one case which was accompanied by a stone in the ureter (fig. 10).

Treatment.—The question of nephrectomy or lithotomy had to be considered in a large number of cases, and the decision was usually not difficult to make. I am more convinced than ever that to remove stones from a kidney which will subsequently contain residual urine, should be avoided if possible. I believe that such a result means inevitably further stone formation, not only on the same side, but with an added risk of it on the other. Unfortunately the state of the opposite kidney sometimes contra-indicates what would otherwise be the proper treatment, namely a nephrectomy. But nevertheless it is sometimes possible to excise the dilated portion of the kidney and thus to remove the opportunity for residual urine to collect.

There have been three different ways in which I have been able to carry this out successfully :—

(1) By resecting a portion of the pelvis.
(2) By resecting the dilated portion of the renal substance.
(3) By resecting the hydronephrotic portion of a double kidney.

In resecting the pelvis I have carried out the Von Lichtenberg technique in three calculus cases as well as in a number of cases of non-calculus hydronephrosis, and the results in not one of these was to my satisfaction. On the other hand a simple resection was completely successful in all of a small number of cases in which it was attempted (figs. 11 and 12).

Resection of the dilated portion of the renal parenchyma in my cases has generally meant amputating the lower pole of the kidney. I regard this as highly necessary and very satisfactory in those cases where nephrectomy is inadvisable. When the portion corresponding to the middle group of calices had to be excised, I found it

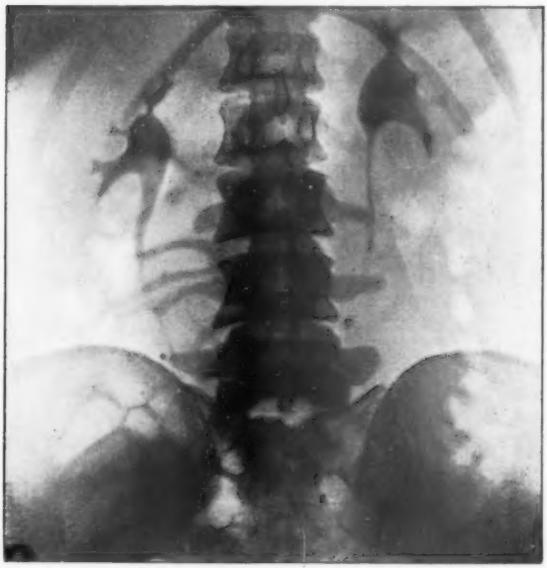

FIG. 5.—Intravenous urogram in a case of left-sided urinary lithiasis. It is to be noted that there is dilatation of both renal pelves.

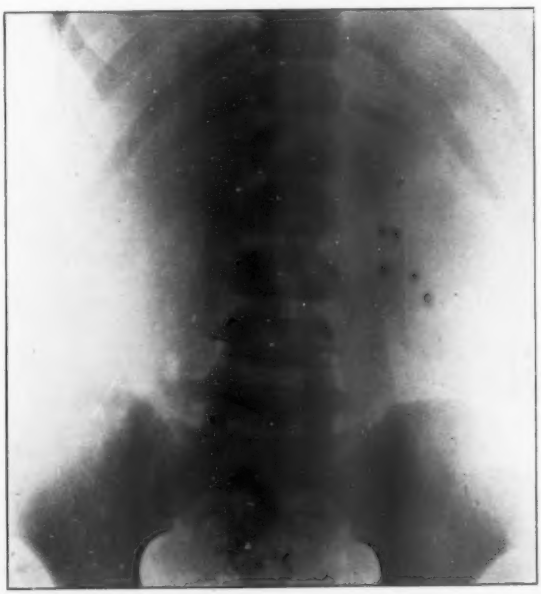

FIG. 6.—Multiple calculi in left renal pelvis in a case of bilateral hydronephrosis in a child aged 8.

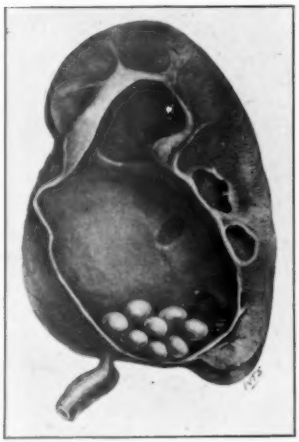

FIG. 7.—A collection of calculi in a left hydronephrosis in a child aged 5 years.

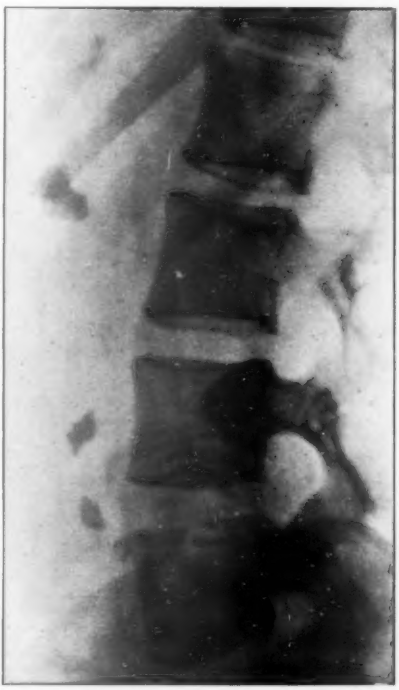

FIG. 8.—A lateral radiogram showing a series of calcified glands in front of the vertebral bodies, but the second shadow from the top is of a stone in the pelvis of a dilated kidney.

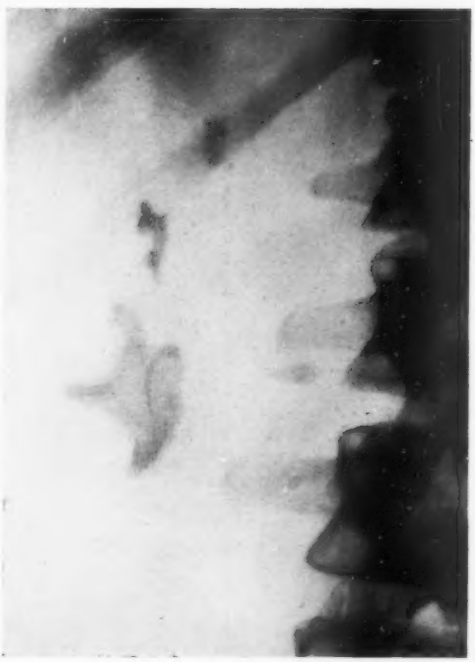

FIG. 9.—Shadows due to calcification in the walls of a renal pelvis and calices in a tuberculous kidney.

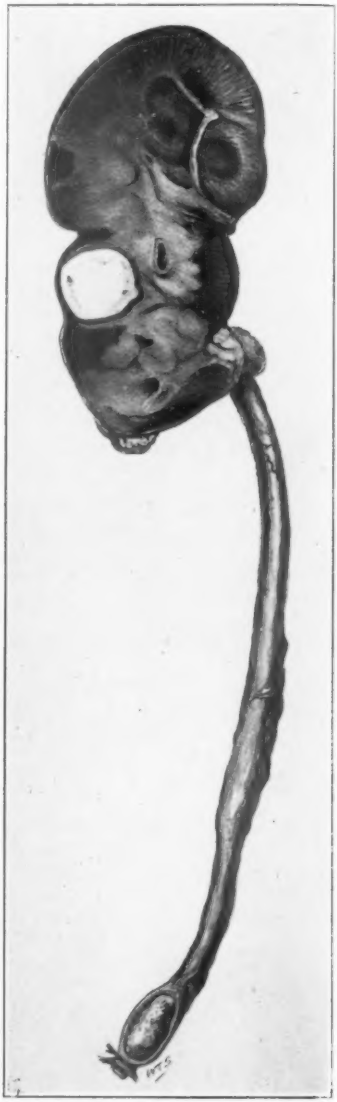

FIG. 10.—A nephro-ureterectomy specimen with a rounded non-tuberculous mass in the kidney and a stone in lower end of ureter.

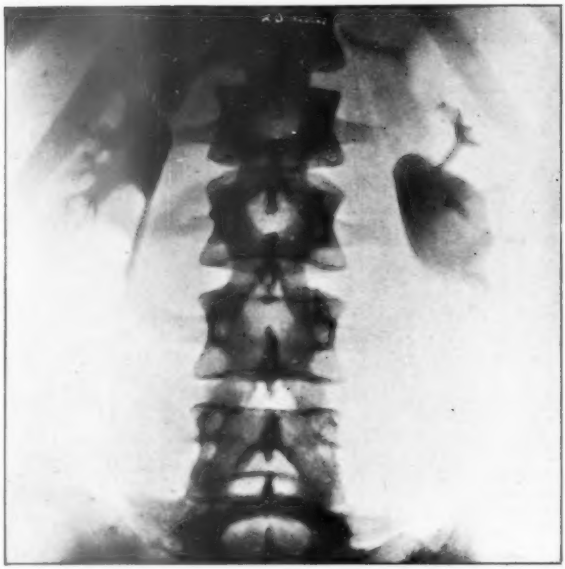

FIG. 11.—An excretion urogram of a left hydronephrosis. There was a small stone in the pelvis.

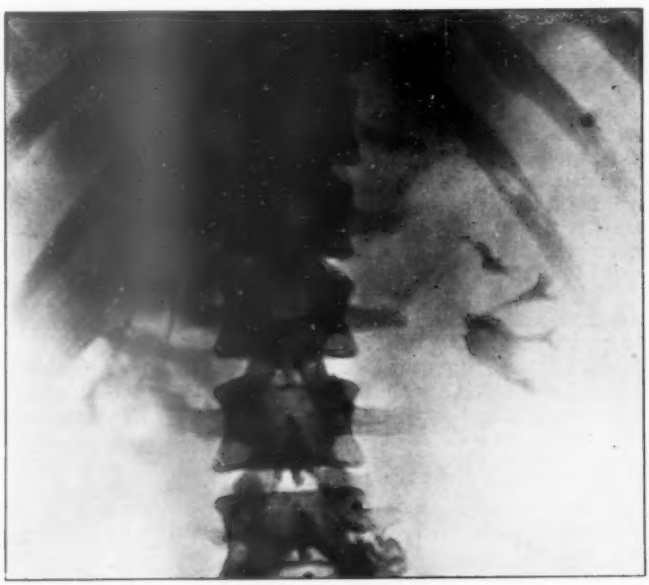

FIG. 12.—An excretion urogram of the same case several months after removal of the stone and resection of the pelvis.

quite adequate to cut away the dilated renal tissue and to drain the kidney through this region for several days. Excision of the hydronephrotic portion of a double kidney presents no difficulties after the blood supply of the healthy portion has been accurately identified and protected.

With regard to nephrectomy my experience makes me feel that in carefully selected cases this form of treatment is most satisfactory, not only because recurrence on the opposite side is uncommon, but because of the tremendous advantage to the patient of a complete riddance of a diseased organ. The subsequent improvement in health is a frequent cause for satisfaction amongst patients of this kind. Although I have no exact figures to give you I can recall a number of cases of recurrence of stone after lithotomy either in the same or the opposite organ, whereas I can recall only one case where stone recurred in the opposite kidney after nephrectomy. In this case fortunately the stone was passed *per urethram*. These conclusions are arrived at as a result of 81 operations of nephro- or pyelo-lithotomy, and 63 cases of nephrectomy which recovered from their operations.

Analysis of 154 operations on 144 cases of renal calculus :—

	No. of operations	Mortality
Pyelo- and nephro-lithotomy	77	2
Pyelo- and nephro-lithotomy and plastic operation on pelvis	6	0
Partial excision of kidney	2	0
Hemi-nephrectomy	1	0
Nephrectomy	61	2
Nephro-ureterectomy	4	0
Nephrostomy	3	0
Total number of operations	154	4

Percentage mortality, 2·5.

It may be a justifiable criticism of these figures that the proportion of nephrectomies is somewhat high. My reply is that results seem to justify such a policy.

Complications of nephrectomy.—There are two particular post-nephrectomy complications of which I have had experience. One is a failure of the ligature to control bleeding from the vascular pedicle, and the other is the development of a colic fistula in the loin wound. With regard to the first I had two cases. In one, after succeeding in getting clamps on the bleeding vessels, the patient was sent back to bed with these still in position ; a week later these were removed without incident. In the other case Marion's method was successfully employed, of pressing gauze firmly into the depths of the wound and keeping up the pressure for five minutes by the clock. At the end of this time the bleeding had stopped, and there was no difficulty in seizing the stumps of the renal vessels.

With regard to post-operative fistula of the colon this occurred following a right nephrectomy in a case of calculous pyonephrosis in a woman aged 51. It was a case where there was known to have been stone in the right kidney for fifteen years and no operative interference had ever been undertaken for it.

The difficulties in separating the kidney from the peritoneum were considerable, but nevertheless neither this nor the bowel was opened, and I am not aware that the latter was even damaged, but its vitality must undoubtedly have been impaired in the course of the dissection. It was a great surprise to me when, about the fifth day, fæces were discharged from the loin. Ultimately intestinal mucosa made its appearance. Fortunately there was no important deterioration of the patient's general condition as a result of the fistula, and as time went on the prolapse of bowel into the wound steadily increased. It became obvious that the condition could only be remedied by opening the abdomen. This in due course was done by a colleague who was a general surgeon. He excluded and removed the affected portion of the bowel with an eminently satisfactory result.

Another most interesting consequence of nephrectomy for stone, which can hardly be called a complication, was the occurrence of a large fatty tumour in the renal fossa. It formed an easily palpable mass in the right loin and gave rise to pain, in a male patient who had had his right kidney removed some years before.

There are other operative complications of which I had experience; the more important of these are (1) secondary hæmorrhage after nephrolithotomy, and (2) the tearing away of the ureter from the renal pelvis as a result of traction on the kidney.

With regard to hæmorrhage I have only had two cases which caused me serious anxiety, in neither did I have to do a nephrectomy and both recovered; both cases were different with regard to the state of the kidney.

(1) The first was a woman aged 21 with extensive bilateral calculus and the bleeding occurred after the one and only operation I carried out, when I cleared out all the stones from the right kidney which I drained for about ten days after the operation. Everything was straightforward up to this point, but the removal of the drain from the kidney initiated an increase of sepsis which culminated in severe renal bleeding. It was finally controlled by blood transfusion and improving the loin drainage as much as possible, and the patient made a good recovery.

In looking back on this case I have no hesitation in saying that permanent nephrostomy would have been the better treatment. It is unlikely that any bleeding would have occurred had I continued my drainage instead of interrupting it.

The other case of secondary hæmorrhage was a man aged 45, who had his hæmorrhage on the seventh day after operation. I had removed a small stone from the lowest group of calices and, in so doing, had cut through a good depth of healthy-looking renal tissue. These are certainly the circumstances likely to lead to a hæmorrhage later on. I was careful to provide good drainage by rubber tissue down to the site of the renal incision, and the drain had not been shortened at the time when the bleeding occurred. I can think of no alternative technique which would have safeguarded against the hæmorrhage. Fortunately it was got completely under control simply by dropping a stitch in the skin, removing all clot from the depths of the wound, and providing more drainage down to the kidney.

(2) The first case in which rupture of the ureter occurred was one in which I had proposed nephrectomy, so no harm was done, but the rupture occurred without my knowledge, and it was certainly disconcerting to find that it could happen so easily. After removing the kidney I did not seek the upper end of the ureter to ligate it, and there followed a most interesting complication, namely, a leakage of urine from the loin wound for about a week. I was surprised to see this as the ureter had not appeared to me to be dilated, and its walls were certainly not rigid as is sometimes the case when such a fistula occurs following nephrectomy for tuberculosis.

What we have to remember, is that in some stone cases the pelvis and adjacent ureter are œdematous, inelastic, and densely embedded, and, in these circumstances, may easily rupture from traction on the kidney.

The second case of rupture was unfortunately one of bilateral renal calculus, and I was exposing the right kidney to remove stones from the pelvis and lower pole. Here I discovered, to my dismay, after delivering the kidney on to the loin, that the ureter had torn away from the pelvis. After removing the stones I re-implanted the ureter into the pelvis by the Von Lichtenberg method. There was a continued urinary fistula for many weeks after this, and I was ultimately forced to perform nephrectomy. On dissecting the kidney later, I found that the union between the ureter and the pelvis was so complete as to entirely obliterate the lumen of the ureter. Fortunately, six months after the removal of stones from the other side, there are still no stones in the remaining kidney, and the urine is free from pus.

This same case afforded one instance of anuria with stone in a single kidney.

After operation the patient was sent to a convalescent home to improve his general condition before removal of the small stone in the lower pole of his left kidney, but unfortunately he had only left hospital a week before he was hurried back again in a condition of anuria. I was out of town at the time, but a colleague passed a catheter up the left ureter and immediately established a flow of urine. It was instructive to observe the effect on the blood urea of the continued ureteric catheter drainage. On admission the blood urea was 245 mgm. per 100 c.c.; six hours after the

passage of the catheter it was 160, and it continued to drop steadily until it reached 20 after six days, when I removed the stone from the renal pelvis. Obviously the patient's ultimate prospects of recovery were immensely improved by the use of the indwelling ureteric catheter.

Operative mortality.—In cases of renal calculus the figures for operative mortality are on the whole satisfactory; my own are: 154 operations with four deaths—a mortality of 2·5%. In two the kidney was opened for the removal of stone, the remaining two were nephrectomies.

The first was a pyelolithotomy in a man aged 45 for a stone about 1½ in. in diameter in the pelvis of the left kidney. Before operation the urine revealed no pus and only a few staphylococci. Some days before the operation an instrument-pyelogram on the left side was carried out; at the operation I resected the 12th rib. The patient developed pneumonia at the right base on the third day, from which he died. On exposing the kidney at operation I found that the pelvis and the lowest calices were somewhat dilated, and turbid urine escaped from the pelvic incision as the stone was being removed.

This incident definitely made me feel that infection in the kidney had been stirred up as a result of the instrumental pyelogram. I doubt very much whether the rib resection had anything to do with his pneumonia as this began in the base of the right lung.

The other case was a man aged 45 who had a stone the size of a sparrow's egg in the pelvis of the right kidney. He was certainly not a good subject. He had had pre-existing urinary tract abnormalities which required surgical treatment; eighteen months previously I had removed a vesical diverticulum and a functionless left hydronephrotic kidney. There was no stone on either side at this time, nor was there at any time the question of dilatation in the right kidney, but a stone developed there in due course nevertheless; the blood urea before his last operation was 81 mgm. %. The left nephrectomy had resulted in a hypertrophied right kidney. At operation extensive adhesions between the upper pole and the diaphragm resulted in a very severe ordeal for the patient, in the delivery of the hypertrophied kidney on to the loin. The patient's blood urea steadily mounted after the operation and was 240 on the third day, and it continued to rise until his death.

The nephrectomy cases that I lost also had extensive perinephric adhesions. They were 38 and 39 years of age respectively, with old-standing and extensive calculi in each of which freeing of the kidney from the surrounding parts was very difficult. My hesitation in not doing a subcapsular nephrectomy in these cases was increased by the knowledge that the thin-walled and infected kidney was certain to be opened on attempting this. On looking back on other cases of subcapsular nephrectomy, one has the knowledge that this method is generally successful, but that there is a prolonged convalescence to look forward to as a result of the continued discharge from the thickened and infected renal capsule which remains.

While recognizing the inevitable risk associated with operating on this type of case, my own experience indicates that if the kidney is especially difficult to free during the operation, changing to subcapsular nephrectomy should be seriously considered there and then in spite of the risk of additional sepsis and a tedious recovery.

There is one point in particular which contributes largely towards success or failure, and that is post-operative drainage in regard to both inside and outside of the kidney. It is important to pay attention to two points in connexion with this, (1) to stitch the drain to the vicinity of the opening in the kidney, and (2) not to remove it for a week.

Before I realized how important these points were, I often noted deep tenderness along the line of the ureter together with constitutional signs of some toxæmia, undoubtedly due to the passage of urine down the outside of the ureter; the clinical signs of this have been conspicuous by their absence with the improved technique mentioned.

The question as to when to drain the kidney itself after a lithotomy is indeed a vexed one. My most successful rules have been not to attempt to drain a kidney

unless there is one of the following conditions: Gross sepsis, considerable local or general dilatation, or anuria. One should take care to incise and drain only through a dilated portion of the organ and to keep the drainage going until the temperature is quite settled. Indeed where the kidney has been considerably dilated it is an advantage to fit the patient with an apparatus so that he can go about with the kidney drainage for months if necessary.

The point of view that a long-continued nephrostomy encourages staphylococcal infection, and therefore further stone formation, seems to be an objection which is more theoretical than practical. The many successful cases of permanent nephrostomy reported in recent years are the best answer to such a criticism.

Recurrence after operation.—The four most important causes of recurrence that I have had personal experience of are the following:—

(1) Leaving behind after operation a dilated and therefore badly draining portion of the kidney.

(2) Leaving behind pieces of stone at operation.

(3) When the stone removed is soft and phosphatic and is therefore accompanied by a high degree of sepsis.

(4) The rapid post-operative formation of soft phosphatic stones which may occur even after the removal of an oxalate stone.

As I have already mentioned, the way to avoid recurrence in the first state, if the kidney must be left behind, is to excise as much as possible of the dilated portion of the organ, or in the worst cases to establish permanent nephrostomy. The best way to avoid the second is to take X-rays on the table during the course of the operation when several small stones are present. This of course is not a complete safeguard, but I have found it a great help. With regard to the third, i.e. soft phosphatic stone, if the kidney must be preserved, the safest course is to establish permanent nephrostomy.

In looking back I can recall several cases of the latter type, and they all had some features in common. The principal of these was that they were all associated with stone in the other kidney.

I would like to make particular reference to the type of case where the recurrence is quick, i.e. within a few weeks of surgical removal. This is almost certainly the soft phosphatic type of calculus. My experience is that one should avoid as long as possible any temptation to reoperate on these cases, for two reasons, namely, that operation is more than likely to result in a nephrectomy, and that if the time can be spared and the stone is in the pelvis, it is very likely to pass. I have had both of these experiences. It is certainly very worrying to have a protracted urinary fistula from the loin, and to demonstrate by X-ray a post-operative obstructing calculus. But such a patient should be got on to his feet as soon as possible and encouraged to drink plentifully, as a result of which he will as likely as not pass his stone.

It is of interest at this stage to state that it is my experience that the majority of patients who have never had an operation for stone, but who pass a calculus following an attack of renal colic seem seldom to be bothered again in this way. The only explanation I can offer for this is that, in such cases, the cause of the stone formation is a transitory one. It also suggests that the retention for any length of time of the stone in the kidney encourages further stone formation.

Bilateral cases.—The incidence of bilateral urinary lithiasis varies according to the different ways in which the matter is studied.

DIFFERENT PERCENTAGES OF BILATERAL CASES ACCORDING TO THE MANNER OF INVESTIGATION

Total number of cases in upper urinary tract ..	12·6%
Renal calculus cases that came to operation	15·2%
Total number of renal calculus cases	17·3%

It seems to me that the important objective in going into this question is to obtain a clear idea as to what extent there is a tendency for the disease to be bilateral. There is no doubt that the figures of the last group are nearer the truth than those of the first two groups. However, to obtain the final word on this subject, it would be necessary to know the post-mortem findings on a large series of renal calculus cases.

The following table gives some details with regard to operations on my cases :—

ANALYSIS OF 32 OPERATIONS ON 22 CASES OF BILATERAL RENAL CALCULUS

	Operations	Mortality
Lithotomy	24	0
Lithotomy and plastic operation on pelvis	1	0
Lithotomy and amputation of lower pole of kidney ..	1	0
Nephrectomy	4	0
Nephrostomy	2	0
	32	0

The treatment of cases with both kidneys occupied by stones at the same time cannot be stated in a few words. Six cases may quite likely require treatment in six different ways according to the particular circumstances in each case.

For instance extensive bilateral calculus in a young person as a rule would require bilateral nephrostomy, whereas the same condition in an elderly person might quite easily require no surgical interference at all.

In one case, a female aged 51, seven years ago I found it justifiable to remove a well-marked pyonephrosis, and two small stones from the calices of the opposite kidney some months later. That patient is in excellent health now and her single kidney is free from stone.

In another bilateral case I removed a stone from each renal pelvis six years ago. There were then stones in both pelves with considerable renal dilatation. The kidneys were tackled separately, and both were drained during the convalescence. Recent radiograms show no recurrence of stone and considerably reduced dilatation.

The type of case already referred to in which there is a stone on one side and a branched calculus forms quickly on the other side in association with a good deal of sepsis, requires permanent nephrostomy at least of the kidney which formed a stone last.

Permanent nephrostomy seems to have been practised very little on this side of the Atlantic. I am personally very favourably impressed with the results of it from my own limited experience. Let me show you a photograph of the apparatus fitted to a patient upon whom I carried out this operation on each side. The patient, a man aged 21 who has had stones removed from both kidneys, still has bilateral calculi. He goes about in complete comfort now and in excellent health (fig. 13).

STONE IN THE URETER

Although the great majority of ureteric calculi undoubtedly come from the kidney, I have had several cases where there was some justification for the conclusion that the stones formed in situ. In each case the appearances suggested a dilatation of the ureter previous to the stone formation. Ureterocele is of course an extreme in this respect. My figures give a definite preponderance in incidence on the left side. In 121 cases, 70 left, 47 right, and 4 bilateral, it is of interest to note that ureteral calculus has occurred in my series twice as often in the male as in the female (male 33, female 38). Indeed in a descending sense it is not till we get to the ureter that it becomes evident how much more common urinary calculus is in the male than the female.

Clinical features.—It has been noticeable how much more frequently colic occurred when the stone was in the upper two-thirds of the ureter than in the lowest third. By the time the stone has arrived in the position outside the bladder, the symptoms were generally nothing more than an aching in the loin. Another point of interest is that it is exceptional not to be able to detect on a plain X-ray any stone in the ureter which gives rise to symptoms. I have had only occasional instances where intravenous urography was necessary to demonstrate the calculus. Phleboliths do not as a rule cause any difficulty with regard to diagnosis, but every now and again the single shadow of a phlebolith calls for careful discrimination.

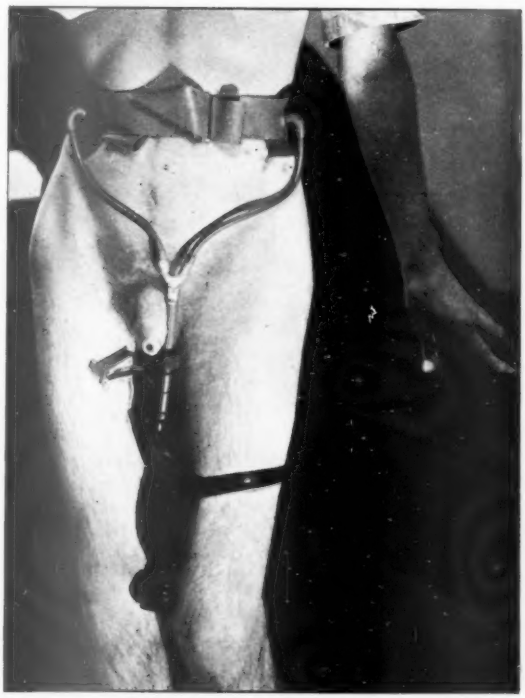

FIG. 13.—A double nephrostomy for bilateral renal calculi.

It may also be said that it is seldom that shadows of calcified glands give any difficulty, but in one case it was wise to continue the investigation beyond the first X-rays.

On the few occasions when I have thought it necessary to pass a wax-tipped bougie up the ureter I have always been satisfied as a result of this procedure that there was no stone present, showing how reliable a good radiogram is in this respect. Cystoscopic appearances of the ureteric orifice when a stone is in the vicinity are sometimes of interest. Here is a contrast in appearances (figs. 14, 15 and 16).

Treatment.—With regard to getting rid of the stone, I have found that the majority of stones in the ureter which have been associated with colic, have passed either

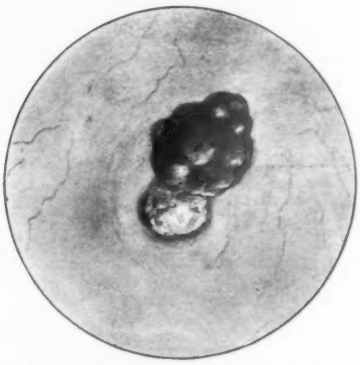

FIG. 14.—Drawing made at the time a calculus was entering the bladder from the left ureteric orifice.

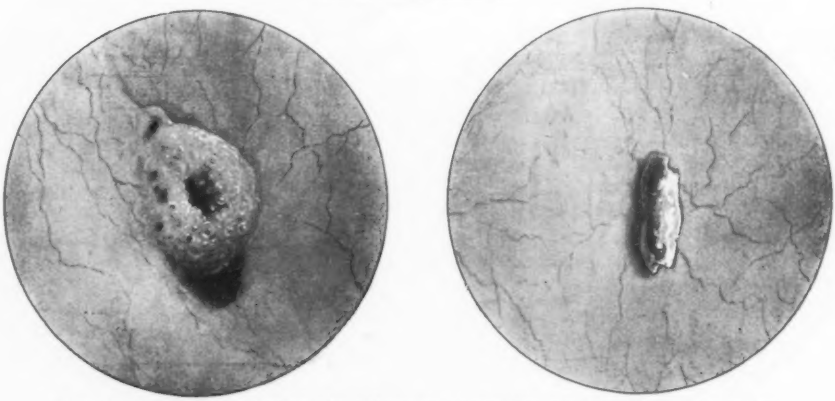

FIG. 15.—Drawings showing the œdematous condition of the left ureteric orifice and the stone which had been recently extruded from it.

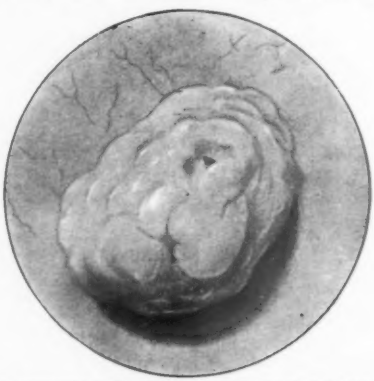

FIG. 16.—Œdematous ureteric orifice with stone impacted behind it. The stone was liberated by incising the orifice with a high-frequency current through a cystoscope.

without any surgical interference, or with the assistance of some procedure which can be carried out through a cystoscope, such as the passage of ureteric catheters and the slitting of the ureteric orifice. A high-frequency and not a coagulating current should be used for this (fig. 16). Only 23% of my 121 cases of ureteric calculi required open operation.

I feel it incumbent at this point to call attention to a special danger in passing instruments up the ureter in the hope of assisting the passage of a stone which is situated in the uppermost third of the ureter. There is, unfortunately, a probability that the calculus will be pushed back into the kidney. If this happens and the stone enters the lowest group of calices, then the whole outlook of the case is altered at once, the probability being that a nephrolithotomy may be necessary where previously there had been no worse prospect than a ureterolithotomy.

It may seem to some that the operative differences are unimportant, but let me remind you that a nephrolithotomy at once introduces the danger of secondary hæmorrhage, and there is, moreover, the difficulty and uncertainty of finding a small stone in the kidney.

Once a stone has reached the pelvic floor, months can be allowed to elapse without the likelihood of serious renal damage and with good prospects that the stone will ultimately pass. This opinion is based on the observations I have made from time to time by intravenous urography, that with the stone in this situation both interference with renal function and the amount of renal dilatation, are relatively slight and diminish as the stone descends.

On the other hand there can be sudden and severe interference with function when a small stone becomes impacted in the upper part of the ureter. In one case when the stone was in the pelvic ureter I waited as long as nine months, with ultimate success. I remember two cases in which the stone had passed into the bladder where I thought this quite impossible from the size of the calculus. I had advised operation in both cases, and in each without any kind of instrumental interference the stone passed into the bladder, where I crushed it. The larger of these was 1 in. $\times$ $\frac{3}{4}$ in. and situated in the sacral portion of the right ureter.

It seems that sometimes a simple cystoscopy will cause an activity of the ureter which results in the evacuation of the stone, and to this I attributed the results in both these cases.

Open operation.—The following is a table giving a brief analysis of the 28 open operations which I carried out for stone in the ureter :—

Ureterolithotomy	19
Nephro-ureterectomy	7
Excision of ureterocele	1
Reimplantation of ureter	1
Total ..	28
Mortality ..	0

As is usual in open operations on the ureter for the removal of stone, the majority were for stone in the lowest third of this passage and in the extramural portion. I have found the approach through an incision above the inguinal region easier than that through the mid-line ; I therefore always employ the former, but were it necessary to remove stones from the lower ends of both ureters at once, I certainly would make use of the latter. In the only case in which this question arose, one stone was coaxed into the bladder by various transcystoscopic manipulations. I had one interesting experience in setting out to remove two stones by open operation from the lower end of a dilated ureter : I had tilted the patient into the Trendelenburg position before the lower end of the ureter was completely exposed, and when I reached the pelvic floor the stones were no longer in the ureter in this situation ; they had undoubtedly

been tipped back into the kidney, but the case was one where there had been a ureterocele and in addition a constriction of the ureter at its junction with the bladder, and this latter condition necessitated a division of the ureter with a reimplantation into the bladder. Fortunately, with the dilated ureter there was no difficulty in leaving the newly constructed orifice of such a width that the stones would be able to pass easily into the bladder ; in due course the patient produced the stones, having passed them *per urethram*.

There is no doubt that renal destruction can be very advanced as a result of the prolonged residence of a stone in the ureter. Eight out of 28 (28·5%) of the open operations which I carried out for stone in the ureter required a nephro-ureterectomy.

Vesical calculus.—To-day the majority of cases of vesical calculus occur late in life ; the average age in my cases was 54·6 years.

Vesical calculus to-day becomes most obvious at the period in life when the various types of bladder-neck obstructions begin to assert themselves, the incidence being overwhelmingly more common in the male. My figures in 87 cases are 84% in this sex. These figures are in striking contrast with those which were published up to the first decade of this century. From these it is obvious that a change in the incidence of vesical calculus is taking place. Freyer, in 1908, in considering the sex incidence in 1,623 patients, found that more than 98% occurred in the male. Hugh Lett, in considering 608 cases of vesical calculus admitted to the London Hospital in the thirty-year period, 1905–34, found that the incidence in the male was reduced to 91%.

My own cases with 84% of males represent a later period still, 1922–38. So that there seems to be good reason for believing that vesical calculus is less frequent in men than it used to be. The most likely cause of this change is that obstructive conditions at the bladder neck are dealt with surgically more frequently than formerly. On the other hand we must not overlook the fact that from the beginning of the century onwards, the more frequent performance of pelvic operations on women may have some bearing on this sex incidence.

Lett is strongly of the opinion, from an analysis of his personal cases, that injury to the bladder during the course of a pelvic operation is the cause of the increase which his figures showed had occurred in women.

On three occasions I have found unabsorbable ligature material inside the female bladder—twice in connexion with vesical calculus. In all cases there had been pelvic operations several years before. In the male simple prostatic enlargement provided the commonest ætiological factor.

Fragmentation of the stone is an interesting condition which I am able to record as a personal experience. I found it in a man aged 82 where there was an associated condition of prostatic hypertrophy. Fig. 17 is a drawing showing the state the calculi were in when I retrieved them from the bladder.

With regard to ætiology the more unusual cases that I have had have been from the debris following electro-coagulation of bladder growth and in association with vesicocolic fistula.

Clinical features and diagnosis.—I need hardly mention that when the stone is in association with prostatic enlargement, symptoms from the stone may be insignificant, and that the less obvious the obstructive condition is, the more pronounced are the symptoms from the stone.

The patient with vesicocolic fistula and vesical calculi had most distressing symptoms by the time I saw him ; there was intense pain on micturition. In this case there were several large stones in the bladder.

The only point I wish to emphasize with regard to diagnosis is that it is dangerous

to rely upon a negative X-ray that no vesical calculus exists. In contrast with the upper urinary tract there is a fairly high proportion of cases of vesical calculi in which a good X-ray film gives no indication that a stone is present. I make the rule of never giving a final opinion on this point without a cystoscopy.

Treatment.—I have already called attention to the high proportion of cases of vesical calculus which are associated with an obstructive condition at the bladder neck. When simple enlargement of the prostate was present, the stone was removed in the course of the procedures carried out for the removal of the prostate. In certain other cases, however, where the obstruction was fibrous, litholapaxy and transurethral resection were employed. After doing these two operations at the same sitting in

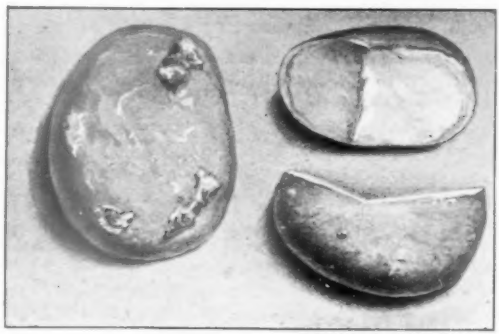

FIG. 17.—Two vesical calculi removed by suprapubic lithotomy. The stone on the right—in two portions—had apparently undergone spontaneous fragmentation.

several cases I gave up this routine and found it more satisfactory to do the litholapaxy first, and not to do the resection until the congestion at the bladder-neck from the manipulation of the lithotrite had settled.

The figures relating to my operations were as follows :—

	Suprapubic lithotomy	Litholapaxy	Removal with Rongeur forceps	Total
No. of cases	40	44	2	86
Percentage	46·5	51·1	2·3	
Mortality	5%	4·5%	0%	

The presence of even a small degree of urethral stricture will wisely be considered as a contra-indication for the use of the lithotrite, the reason being that the continued urethral instrumentation can so easily be the means of stirring into activity the latent infection which is inevitably present in the tissues in the vicinity of a urethral stricture. I had the experience in one case where although the stricture was only mild in character and offered no obstruction to the passage of the lithotrite, the consequent infection resulted in a peri-urethral abscess and fistula, which later required repair.

In looking back on the cases that died after litholapaxy, I cannot help feeling that the best safeguard against fatalities is to make ample use of indwelling catheter drainage, both before and after operation. Pre-operatively this is particularly advisable if renal function is bad, or bladder sepsis marked. After operation this

form of drainage should be continued in the presence of the same complications until these have gone.

Urethral calculi.—I dealt with 11 of these cases and the outstanding features have been as follows :—

Most commonly in the prostatic urethra, 55%.
Associated with urinary calculus elsewhere, 62%.
The absence of acute symptoms.
The toleration of the stone in the urethra for long periods.
The slow increase of local symptoms with the passage of time.

The treatment varied widely according to circumstances, as follows :—

External urethrotomy.
Suprapubic lithotomy.
Stone pushed from prostatic urethra to bladder and there crushed.

There was no mortality from these procedures.

Prostatic calculi.—I feel that there are good reasons for considering prostatic and urinary calculi together, for the two conditions are not only often associated, but the chemical composition of the stones in the two situations is often the same. Treatment is just as successful by complete removal of the gland as prostatectomy is for adenomatous prostate, the outstanding requirement in both cases is the same, namely adequate pre-operative bladder drainage, either entirely by indwelling catheter or by suprapubic cystostomy.

When I say that treatment is satisfactory, I mean with regard to mortality and recurrence of stone. I have carried out prostatectomy in 12 of these cases, 5 in one stage and 7 in two stages. I am not aware of recurrence of the lithiasis is any of them. In three other cases where the calculi were insignificant I relieved the obstruction by transurethral resection with the electrotome. There were no deaths from any of these operations ; one should keep in mind in the prostatectomy cases the tendency to post-prostatectomy obstruction. I have noted this in several of mine. The best safeguard that I have found is to stitch the margin of the prostatic cavity to its floor. Alternatively contraction of the bladder neck can be prevented by intermittent dilatation, or transurethral resection at a later date, but I have never had to carry out this last procedure in any of my cases.

Section of Surgery

President—C. H. S. Frankau, C.B.E., M.S.

[*November* 16, 1938]

Malignant Degeneration of Gastric Ulcer

By Professor H. Finsterer (Vienna)

(*From the first surgical department of the Allgemeines Krankenhaus in Vienna*)

Abstract.—Malignant degeneration is the most serious complication of gastric ulcer. Its recognition is difficult both in the early stage and in advanced cases in which only the evidence of a previous ulcer-cavity, and the radiating folds of the mucous membrane indicate progressive development of carcinoma from an original ulcer.

It is impossible to say how often gastric ulcer becomes malignant; one can only state the frequency of ulcer-carcinoma, found in gastric resections.

One hundred and forty-one personal cases of ulcer-carcinoma are recorded, and are divided into three groups.

Group I: 41 which were diagnosed clinically and at operation as cases of ulcer, but in which histological examination showed incipient cancer.

Group II: 55 diagnosed clinically as cases of ulcer, but in which a diagnosis of ulcer-carcinoma was made during operation and afterwards histologically confirmed.

Group III: 45 diagnosed both clinically and macroscopically (from the typical folding of the mucous membrane) as cases of ulcer-cancer, in which the cancer had entirely overgrown the ulcer.

Therefore in the series of 532 resections for gastric ulcer the frequency of ulcer-carcinoma was 20·9%, or 15·2% if the third group is omitted.

In a series of 718 resections for gastric cancer, the frequency of ulcer-carcinoma was 19·6% (or 14·2% if the third group is omitted).

The mortality in simple two-third resection of the stomach is low (four deaths in 99 cases = 4%). When the pancreas, liver, colon, or œsophagus, is involved, the resection mortality is high (14 deaths in 42 cases = 33·3%), but even in these cases the operation is justifiable because permanent cures were achieved in a number of cases.

The prognosis in cases of ulcer-cancer is very grave. In many cases, judging from the author's own experience, patients suffering from incipient ulcer-cancer—only histologically diagnosed as cancer—die from liver metastases, in spite of radical resection. It will thus be seen that the end-results of resection for ulcer-carcinoma are actually worse than those of resection for primary carcinoma.

A. Ulcer-cancer: In Group I, 35 cases were operated on before 1933, and in 18 of these (51·4%) the patients have been free from symptoms for more than five years; in Group II, 27 cases were operated on before 1933, and in four of these (14·8%) the patients are still symptom-free. In Group III, out of 37 cases operated on, only two patients (5·4%) have been symptom-free for the same period.

B. Primary cancer: Out of 260 cases of resection for primary cancer before 1933, 77 patients (29·6%) are permanently cured.

If the ulcer-cancer is so far advanced that the diagnosis can be made clinically, or during operation, the prognosis is extremely bad (permanent cures having been only 9·3% in the series).

In cases of gastric ulcer the best plan is to carry out resection before malignant degeneration begins. The result would then be that not merely 51% but at least 90% of the patients would be alive and well after five years.

RÉSUMÉ.—La dégénération maligne est la complication la plus grave de l'ulcère gastrique. Elle est difficile à reconnaitre aussi bien à son stade initial que dans les cas avancés où seulement l'histoire d'une niche ulcéreuse dans le passé et les plis radiaux de la muqueuse indiquent le développement progressif du cancer sur l'ulcère original.

Il est impossible de décider la fréquence de la dégénération maligne de l'ulcère gastrique. On ne peut que constater la fréquence du cancer ulcéreux trouvé à l'occasion d'une résection de l'estomac.

L'auteur rapporte 141 cas personnels de cancer à base d'ulcère. Il les classifie en trois groupes :

Group I : 41 cas où le diagnostic d'ulcère gastrique fut posé cliniquement et pendant l'opération, mais où l'examen histologique révéla un cancer commençant.

Group II : 55 cas où le diagnostic d'ulcère fut posé cliniquement, mais où le diagnostic de cancer fut posé à l'opération et confirmé par l'examen histologique.

Group III : 45 cas où le diagnostic clinique et macroscopique de cancer à base d'ulcère fut posé, d'après les plis caractéristiques de la muqueuse, et où le cancer avait complètement oblitéré l'ulcère.

Dans cette série de 532 résections pour ulcère gastrique la fréquence du cancer à base d'ulcère fut donc de 20·9%, où 15·2% si le troisième group est omis.

Dans une série de 718 résections pour cancer de l'estomac la fréquence du cancer à base d'ulcère fut de 19·6% (ou 14·2% en omettant le troisième groupe).

La mortalité de la résection simple de deux tiers de l'estomac est faible (4 fatalités sur 99 cas = 4%). Quand le pancréas, le foie, le colon ou l'œsophage sont inclus dans la résection la mortalité est beaucoup plus haute (14 fatalités sur 42 cas = 33·3%), mais l'opération est quand meme justifiée, car un certain nombre de guérisons permanentes ont été obtenues.

Le pronostic du cancer à base d'ulcère est très grave. D'après l'expérience de l'auteur, beaucoup de malades portant des cancers commençants à base d'ulcère, révélés seulement par l'examen histologique, succombent à des métastases au foie même après une résection radicale. On voit donc que les résultats finaux de la résection pour cancer à base d'ulcère sont même pires que ceux de la résection pour cancer primitif.

A. Ulcero-cancer : Parmi 35 cas du premier groupe opérés avant 1933, 18 (51·4%) sont guéris depuis plus de 5 ans. Parmi 27 cas du second groupe opérés avant 1933, 4 (14·8%) sont encore en bonne santé. Parmi 37 cas du troisième groupe opérés avant 1933 seulement 2 sont en bonne santé à la fin de 5 ans.

B. Parmi 260 cas de résections pour cancer primitif opérés avant 1933, 77 opérés (29·6%) sont guéris en permanence.

Si le cancer à base d'ulcère est avancé au point que le diagnostic peut être posé cliniquement ou pendant l'opération, le pronostic est très grave, car une guérison permanente n'a été obtenue que dans 9·3% des cas dans cette série.

Dans tous les cas d'ulcère gastrique le meilleur traitement est la résection avant le commencement de la dégénération maligne. De cette façon la proportion des guérisons durant plus de 5 ans pourrait etre augmentée de 51% à au moins 90%.

ZUSAMMENFASSUNG.—Die maligne Degeneration des Ulcus ventriculi ist die schwerste Komplikation, deren Erkennung schwierig ist im Beginn und in den vorgeschrittenen Fällen, wo nur der frühere Nachweis einer Ulcusnische und die radiäre Faltung der Schleimhaut die Entwickelung des Karzinoms von eimen alten Ulcus erkennen lassen.

Es ist unmöglich festzustellen, wie oft das Magengeschwür malign degeneriert, man kann nur feststellen, wie oft bei der Magenresektion ein Ulcus Carcinom gefunden wird.

Das eigene Material umfasst 141 Fälle von Ulcus Carcinom, die in 3 Gruppen eingeteilt werden :

Gruppe I : 41 Fälle, mit der klinischen und Operationsdiagnose : Ulcus callosum, wo erst bei der histologischen Untersuchung das beginnende Karzinom gefunden wurde.

Gruppe II : 55 Fälle, bei welchen die klinische Diagnose Ulcus war, wo aber bereits während der Operation die maligne Degeneration erkannt und dann histologisch bestätigt wurde.

Gruppe III : 45 Fälle, in welchen die Diagnose Ulcus Carcinom durch den klinischen Verlauf und den makroskopischen Befund (radiäre Faltung der Schleimhaut) sicher war, wo aber das Carcinom das ganze Ulcus überwuchert hatte.

Die Frequenz des Ulcus Carcinomes ist daher bei 532 Resektionen wegen Ulcus ventriculi 20·9% oder nach Abzug der 45 Fälle der III. Gruppe 15·2%.

Bei 718 Resektionen wegen Magenkrebs war die Frequenz des Ulcus Carcinoms 19·6%, oder nach Abzug der III Gruppe 14·2%.

Die Mortalität ist bei der einfachen 2/3 Resektion des Magens gering (99 Fälle mit 4 Todesfällen = 4%). Bei gleichzeitiger Resektion von Pankreas, Leber, Colon oder Oesophagus ist die Mortalität hoch (42 Fälle mit 14 Todesfällen = 33·3%), trotzdem ist auch in diesen Fällen die Operation berechtigt, weil damit in einer Anzahl von Fällen eine Dauerheilung erzielt werden konnte.

Die Prognose des Ulcus Carcinoms ist schlecht. Nach persönlicher Erfahrung sterben Patienten mit beginnender maligner Degeneration, wo das Carcinom erst bei der histologischen Untersuchung festgestellt werden konnte, trotz Radikaloperation bald an Lebermetastasen. Dabei sind die Daurresultate schlechter als nach der Resektion eines primären Magenkrebses.

A. Ulcus Carcinom: In Gruppe I sind von 35 Patienten, die vor 1933 operiert wurden 18 Patienten (= 51·4%) über 5 Jahre rezidivfrei geblieben; in Gruppe II sind von 27 Fällen 4 Fälle = 14·8% dauernd geheilt, während von 37 Fällen der Gruppe III nur 2 Patienten = 5·4% über 5 Jahre geheilt geblieben sind.

B. Primär Carcinom: Von 260 Resektionen wegen primären Carcinom sind 77 Patienten = 29·6% dauernd geheilt. Wenn das Ulcus Carcinom so weit vorgeschritten ist, dass die Diagnose Carcinom nicht blos klinisch, sondern auch bei der Operation bereits gestellt werden kann, dann ist die Prognose sehr schlecht (nur 9·3% Dauerheilung).

Beim Magengeschwür ist es am besten, zu resezieren, bevor es zur malignen Degeneration kommt, dann würden nach 5 Jahren nicht 51% sondern mindestens 90% vollkommen gesund leben.

MALIGNANT degeneration of a gastric ulcer is the most serious development, much worse than either acute perforation or acute, profuse hæmorrhage; as it may end fatally not only through operation but also through the frequent subsequent development of metastases after a radical operation.

Since the researches of Hauser, the possibility of malignant degeneration of a gastric ulcer is generally accepted, but there is a wide difference of opinion as to its frequency which greatly influences operative indications. Aschoff's doctrine of the very rare occurrence of such malignant degeneration is well known, and is quoted from time to time in textbooks and other publications. But it is not equally well known that he retracted his doctrine at the Congress of Pathologists in Würzburg in 1925. Stimulated by the work of Stoerk, Aschoff re-examined the specimens which his pupils Strohmeyer and Peyser had declared to be ulcerated primary cancer, and was able to determine that with but one exception all of them were malignant degenerated primary ulcers. In the interesting paper published by Newcomb are tabulated 100 views of the incidence of ulcer-cancer, which varied from 0 to 90%. He explained that the great difference in the frequency was due to the divergent interpretation of the heterotypical epithelial proliferation at the edge of the healing ulcer which was considered early cancer by some of these examiners.

It will never be possible definitely to establish how often the gastric ulcer undergoes malignant degeneration, because it would be necessary in a given country not only to establish without question the clinical diagnosis of gastric ulcer, but also to follow up all these patients for life. Therefore the percentage can be estimated only approximately, in a number of ways.

The examination of the post-mortem specimen is the least satisfactory of all to establish the incidence of ulcer-carcinoma, even though such examination can be performed most thoroughly. Should a patient die as a result of an ulcer-carcinoma, then the malignant growth has completely overgrown the ulcer so that it no longer can be recognized as an ulcer-carcinoma; should, however, the patient die from some other cause, then it is possible to recognize from the post-mortem specimen an accidental finding of an ulcer-cancer.

Of greater value is the examination of the operative specimen by an able and experienced pathologist, able to recognize early degeneration. The wide difference (5 to 50%) can be explained by the variation in patients operated upon, and by a variation in the thorough examination of the specimens. A surgeon who refuses to operate upon acute flat ulcers, but who operates on chronic ulcers of long standing, resecting all gastric ulcers even those near the pylorus and penetrating into the pancreas, lesions which so often are dismissed with only a gastro-enterostomy, such a surgeon will have a higher incidence of malignant degeneration than the one who promptly operates on acute ulcer, who resects small flat ulcers which rarely degenerate, and who leaves behind the large callous ulcer penetrating into the pancreas due to the increased operative risk.

Histological examination should be performed by an experienced pathologist, not by the surgeon, because it so largely determines the percentage of incidence of ulcer-carcinoma. It is exceedingly difficult to differentiate early cancer from the heterotypical epithelial proliferation at the edge of a healing ulcer. Years of experience are necessary to do this. Also, occasionally it is difficult to locate the point of malignant degeneration, even though the malignancy has already been found in the lymph-gland, because it is impracticable to examine each ulcer in serial section. Macroscopically it is rarely possible to recognize early malignant degeneration by the round and indurated edges of the ulcer, and the increased redness and fixation of the mucous membrane to the underlying tissue. Moreover, cases are not so infrequent where, despite a thorough examination that failed to reveal carcinoma, the patient died one or more years later with metastases in the liver, though no gastric malignancy could be demonstrated at post-mortem. By re-examination of the preserved operative specimen the point of malignant degeneration could be determined. Such observations have been reported by Haberer, Rixford, and others. When these patients remain permanently cured they cannot be included in the list of ulcer-carcinomas.

Sixteen years ago I operated upon a 51-year-old patient who came to me with a history of gastric trouble of twelve years' standing, and with pains, loss of appetite, loss of weight for six weeks. X-ray examination revealed a niche the size of a hazel-nut in the lesser curvature. Blood was present in fæces. The operation was performed under splanchnic anæsthesia on September 2, 1922. A gall-bladder filled with stones was removed and subtotal gastrectomy with resection of a part of the pancreas was done, for a penetrating ulcer near the cardia suspicious of malignant degeneration. Histological examination (Stoerk) showed a typical peptic ulcer. Some months later Moszkowicz happened to re-examine this specimen and found a point of early tubular carcinoma, which diagnosis was confirmed by Stoerk. The patient is still alive, sixteen years after operation.

In February 1937 I operated on a 44-year-old man, who from 1934 onwards had been treated for a gastric ulcer by well-known physicians in Berlin and London without permanent success. X-ray examination showed a small ulcer niche in the middle of the lesser curvature. There was marked hyperacidity, and frequent vomiting. At the operation, a callous ulcer the size of a walnut, and not suspicious of malignant degeneration, was found in the lesser curvature. A typical two-third resection was performed, with uneventful recovery. The histological examination by Prof. Chiari showed a typical callous ulcer, but carcinoma in the lymph-glands prompted him to ask me whether the patient had a primary cancer in the pancreas. Only after examining the different points of the margin of ulcer was there found early malignant degeneration in the form of a carcinoma simplex infiltrans. The patient gained in weight, was doing well for three months; then he started to have severe pains in his back radiating into the legs, showed progressing cachexia and jaundice through metastasis in the liver, and died five months after the operation in the Cancer Hospital of London.

According to Stoerk malignant degeneration always begins in the margin of the ulcer and often in a number of points simultaneously; extending later to the submucosa and muscularis propria, so that the base of the ulcer is the last to be involved

because of the scar tissue there. In an advanced case the entire ulcer is overgrown so that it is difficult and often impossible to determine histologically that the malignant growth originated in an ulcer. Sometimes in this type of case it may be possible to demonstrate in the rest of the ulcer the breakdown of the muscularis mucosæ and muscularis propria and its replacement by scar tissue. These advanced cases can be positively diagnosed during the operation as malignant because the carcinoma has already involved the serosa, resulting in the characteristic picture. The radiating folds of the gastric mucosa toward the carcinoma suggest the conclusion that a chronic, long-standing, ulcer, preceded the cancer, which deduction is supported by previous X-ray and clinical examination, periodic pains, severe hæmorrhages, &c. Even fifteen years ago Stoerk placed great emphasis upon these radiating folds in the gastric mucosa, declaring that they were present only in chronic callous ulcers or ulcer-cancer, and never in ulcerated primary cancer. Since Stoerk drew my attention to this important finding, I have been able to demonstrate these radiating folds in all cases of gastric carcinoma that had a long-standing ulcer history, even though the pathologist could no longer prove histologically the origin of the carcinoma from an ulcer. I will now demonstrate the macroscopic picture of such a case.

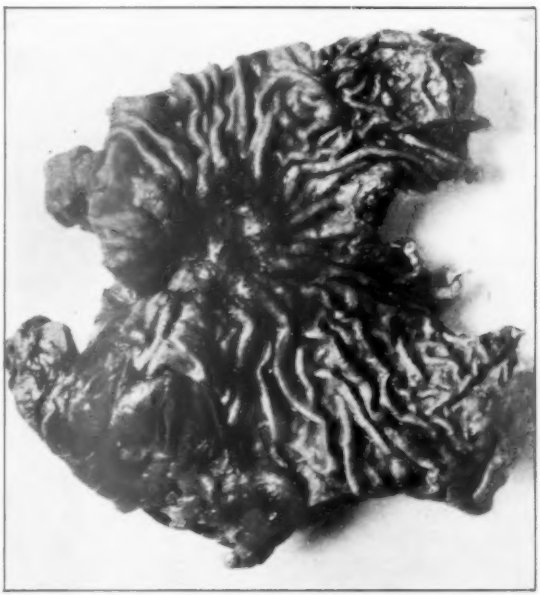

FIG. 1.—Ulcer-carcinoma of the stomach showing folds of the mucous membrane radiating towards the old ulcer.

A 62-year-old man had been ill for twenty-six years, treatment giving only temporary relief. Twenty years ago the ulcer niche had been demonstrated radiologically, on the lesser curvature near the pylorus. Over a number of years he had had five severe hæmorrhages, severe pains periodically, and vomiting. For six months there was loss of appetite and weight, and increased vomiting. The hyperacidity continued (HCl 40, total acidity 70). Radiological examination showed an enormously dilated stomach with retention of gastric contents for twenty-four hours due to the nearly complete pyloric stenosis. At the operation malignant degeneration of the

gastric ulcer penetrating into the pancreas was established without question, for the neighbouring lymph-glands were hard and enlarged. Subtotal gastrectomy with resection of part of the pancreas was performed. The specimen showed the macroscopic picture of an old callous ulcer or an ulcer-carcinoma, with radial folds of the gastric mucosa. The microscopic examination of the specimen showed such extensive overgrowing of the whole base of the ulcer with carcinoma that histological diagnosis of ulcer-carcinoma was no longer possible.

It is generally accepted that only the gastric ulcer, almost never the duodenal ulcer, undergoes malignant degeneration. I have never even once found in more than 1,500 cases a duodenal ulcer that had undergone malignant degeneration. Also Pauchet never once found malignant degeneration in a duodenal ulcer, whereas Haberer, and Moynihan, each observed two. Therefore, in stating the frequency of malignant degeneration of an ulcer we are obliged to omit the duodenal ulcer. Why a duodenal ulcer fails to undergo malignant degeneration is not known. Even though one does not have to fear malignant degeneration in a duodenal ulcer, one must remember that a co-existing gastric ulcer overlooked by the radiologist can nevertheless become malignant.

Seventeen years ago I had to operate upon a 33-year-old man for a severe hæmorrhage from a stenotic duodenal ulcer. He also had a callous prepyloric ulcer, the histological examination of which showed early carcinoma, partially infiltrating. The patient remained well for eight years, dying finally from a meningitis, that followed periostitis of the mandible.

My statistics of resected ulcer carcinoma show 141 cases. 41 were operated on for gastric ulcer. Of these only one, a 49-year-old-man, died, of pulmonary embolus, and all the others recovered. In 55 cases it was possible to recognize the malignant

TABLE I.—ULCER-CARCINOMA.

Malignant degeneration found	Number	Mortality
(1) Only by histological examination	41	1 = 2%
(2) During the operation and by histological examination	55	11 = 20%
(3) Only clinically and macroscopically proven ..	45	6 = 13·3%
Total ..	141	18 = 12·7%

degeneration during the operation, which was later confirmed histologically. In these cases not only was the great omentum removed, but also in penetrating ulcers parts of the pancreas or liver or colon were resected too. In this group the mortality was 20%. In 45 cases the diagnosis of ulcer-carcinoma was only established by the history, clinical findings, and examination, of previous repeated X-ray pictures, which showed the ulcer niche. The resected specimen macroscopically showed the characteristic radiating folds which proved its origin from an ulcer, but histologically this origin could not be proved as it was overgrown by the carcinoma. Six of these cases died = 13·3%.

During this period 532 resections for gastric ulcer had been performed. The frequency of ulcer-carcinoma was 20·9% in these cases ; if the 45 cases are subtracted in which it was no longer possible to prove the origin from an ulcer, then the frequency is 15·2%.

TABLE II.—FREQUENCY OF ULCER-CARCINOMA.

Resection for gastric ulcer.. ..	532	Resection for ulcero-cancer	141 = 20·9% (96 = 15·2%)
Resection for primary gastric cancer	577	Resection for ulcero-cancer	141 = 19·6% (96 = 14·2%)

Of 718 resected carcinomas, in 96 cases the origin from an ulcer was proved histologically, and in 45 cases clinically. Therefore the frequency of ulcer-carcinoma compared with the resection for primary cancer is 14·2% or 19·6%. Besides these,

15 cases of inoperable ulcer-carcinoma were observed, in four cases of which the diagnosis was confirmed by the post-mortem and subsequent histological examination. With private patients, in my experience, the incidence of ulcer-carcinoma is greater than in hospital cases, because the latter are sent earlier to operation for their gastric ulcer.

Konjetzny maintained that the high percentage (24%) of malignant degeneration in my statistics can be explained by the fact that—(1) cases of ulcerated primary cancer were diagnosed as degenerated ulcers, and (2) that cases with atypical epithelial proliferation at the border of a healing ulcer were diagnosed histologically as early cancer.

The diagnosis was never made by myself but always by a competent pathologist, at first by Stoerk, one of the most experienced of gastric histologists, and after his death by Theodor Bauer, Chiari, Maresch, and Sternberg, who are responsible for the diagnosis. It is generally considered difficult to differentiate beginning cancer from atypical epithelial proliferation. That Stoerk's diagnosis of early cancer was correct is proved by two cases, the histological findings of which were demonstrated in the Medical Society, where the diagnosis was questioned by Sternberg. However, both patients died within twelve and fifteen months respectively with metastases in the liver, while the autopsy failed to reveal any new carcinoma that could have caused such metastases.

Takat's reports from Verebely's Clinic a 25% incidence of beginning malignant degeneration of all the resected gastric ulcers, and Spakkukotzky found even 40% of ulcer carcinoma which prompted him to declare that the gastric ulcer is a precancerous lesion and its resection an early operation for cancer. In the literature I am quoted as saying that 24% of all gastric ulcers undergo malignant degeneration. This is wrong ; what I did say was that in 24% of my gastrectomies for gastric ulcer, an ulcer-carcinoma was found. This figure should not be applied generally because only a small number of patients with gastric ulcer are operated on ; and furthermore my cases were often unusually difficult, and some of my patients came from other countries.

The frequency of malignant degeneration has been calculated from following up those who had had gastro-enterostomy performed. In this way Loehr reported from the records of the Anschuetz Clinic a frequency of 1·7% (corrected 2·6%) in support of his contention that malignant degeneration is exceedingly rare. If such figures are obtained from gastro-enterostomy cases, then one must exclude not only those with duodenal ulcer but also those with so-called cicatricial pyloric stenosis. In my experience this often develops through hypertrophy of the pylorus in cases of ulcer in the posterior wall of the duodenum. Moreover, one cannot exclude those cases that die from carcinoma within two years after operation, as Loehr did, with the assertion that at the operation primary cancer was already present, despite a long history of ulcer. Finally, one can compare the number of patients who died from cancer after a gastro-enterostomy only with those who were not cured by a gastro-enterostomy. Healed cases rarely undergo malignant degeneration ; according to Hurst carcinoma never develops on the base of a healed ulcer scar. As Loehr had 22% uncured cases out of 113 gastro-enterostomies, of which nine later died with carcinoma, it follows that his ulcer carcinoma incidence is not 2·6% but 30%. The same holds true for the statement made by Reischauer from Kuettner's Clinic. It is interesting that Balfour, of the Mayo Clinic, reported from following up patients, that the later death-rate of patients after operation for duodenal ulcer corresponded to the normal death-rate, while the later death-rate, after operations for gastric ulcer, was three times as large as the normal rate, and 40% of these latter were due to carcinoma.

The percentage figures are not really important provided that the general practitioner and even some physicians do not thereby conclude that a gastric ulcer should

not be operated upon because of the danger of malignant degeneration, and that gastro-enterostomy will suffice if operation becomes necessary for a stenosis. Bailey believes that this is the cause of the increased incidence of ulcer carcinoma because he knows general practitioners who during ten years of busy practice have not once had a patient operated on for gastric ulcer. I have in my records of ulcer-carcinoma a number of instances where the family doctor or the physician kept on treating the gastric ulcer and advising against operation, until finally the condition either became inoperable or required an exceedingly dangerous operation. Two such are worth quoting.

A 50-year-old man had ulcer symptoms since 1919, and an ulcer niche had repeatedly been demonstrated on the lesser curvature. His two brothers had been operated upon by me for duodenal ulcer and had been permanently cured. This patient also wished to be operated upon but his physicians in Prague advised against this as being too dangerous, and that healing could be effected without an operation. In February 1924 he was examined by Professor Dr. Julius Bauer, who referred the patient to me with the diagnosis of gastric ulcer. At the operation performed February 29, 1924, under splanchnic anæsthesia, a callous ulcer, wholly unsuspected of malignancy, was found on the lesser curvature near to the pylorus. A typical two-third resection was performed, without removing the greater omentum. Recovery was uneventful. On the third post-operative day Prof. Bauer received a letter from the family doctor reproaching him for having recommended so dangerous an operation, as it was only a simple gastric ulcer which had always been effectively controlled with medical treatment; and could again have been so managed. The histological examination of the specimen by Prof. Stoerk revealed to our surprise early degeneration at one point of a typical callous ulcer, though in such an early stage that the diagnosis of cancer was questioned by a number of pathologists, including Prof. Sternberg. The patient recovered quickly, gained 15 kilos 30 lb. and was completely well for one year. Then he developed jaundice due to metastases of the liver, and three months later he died. The autopsy showed massive metastases of the liver, but the stomach stump was perfectly normal, and no other signs of primary cancer.

If this patient had been operated upon even six months earlier, he would be alive and well to-day as are his brothers, sixteen and eighteen years respectively after operation.

A 49-year-old patient from Poland had been ill since 1926. In December 1926 a prepyloric ulcer with a niche had been demonstrated. The patient was under the care of Prof. Kuttner of Berlin, a very experienced gastro-enterologist. Because of the recurrences and the necessary rest cures the patient, in June 1928, wished to be operated upon, but his family doctor advised against this. In November 1928, a relative of his who had suffered twenty years with a duodenal ulcer had fully recovered after resection, and the patient again wished to be operated upon but was dissuaded by the physician, who assured the patient's wife that not only was the operation unnecessary but that cancer was not present and would never appear. In March 1929 loss of appetite and marked anæmia followed a dietetic indiscretion, and symptoms of marked hyper-acidity persisted. In May 1929, re-examination by X-ray showed there was now an irregular filling defect at the point of the niche, for which the family doctor advised operation. At the operation performed May 25, 1929, under splanchnic anæsthesia, a large callous ulcer in the lesser curvature penetrating the left lobe of the liver was found. The neighbouring lymph-glands were enlarged. Gastrotomy and palpation showed a callous ulcer with indurated, irregular outline, so that the diagnosis of malignant degeneration could be made. Therefore it was necessary to perform a subtotal gastrotomy with resection of a large portion of the left lobe of the liver. Histological examination showed a highly differentiated cylindrical-celled carcinoma, with the liver infiltrated with the same carcinoma, which was found in all the removed glands. The patient recovered from this extensive operation, although a biliary fistula persisted for some time. He gained until his weight became normal. That patient is well to-day, nine years after the operation. If he had been operated upon one year previously, only a penetrating ulcer would have been found, and resection of the liver avoided.

The diagnosis of early malignant degeneration is almost impossible with the ordinary examination. In the advanced stage, when hyperacidity disappears, loss of appetite develops, and the patient begins to look badly, then cancer is suspected. The patient is then operated on, but with a poor chance of permanent cure. Radiological examination can never establish the diagnosis of early malignant degeneration, despite the claims to the contrary, for one cannot even do that from the macroscopic inspection of the specimen. When finally an irregular filling defect is found at the site of a previous ulcer-niche, then the lymph-glands are involved and the operation is too late.

Many examiners attach great significance to size of the ulcer-niche in differentiating it from a cancer. According to Alvarez and McCarty ulcers are rarely larger and carcinomas rarely smaller than 2·5 cm. in diameter. Bloomfield, however, has proved that 23% of resected carcinomas were smaller than 2½ cm. According to my experience it is impossible to differentiate an ulcer from primary carcinoma from the size alone, because I have not infrequently removed a gastric ulcer from 5–10 cm. in diameter penetrating into the pancreas, and I once had occasion to resect a gastric ulcer penetrating into the pancreas which extended from the pylorus to the cardia, and which was 12 by 4 by 2 cm.

Whether gastroscopy can help to differentiate an ulcer from a small primary cancer, remains to be seen. The characteristic induration of the border of the ulcer cannot be recognized by gastroscopy, nor can the fixation of the mucous membrane. Perhaps, with the gastroscope, it is possible through the recognition of specific shades of colour in the mucous membrane to recognize early malignant degeneration.

During the operation it is hardly possible to ascertain malignant degeneration in the early stages, because palpation alone of the borders of the ulcer through gastrotomy is too indefinite. The advanced cases permit of diagnosis during the operation because the carcinoma has infiltrated under the serosa and because the palpating finger introduced through the gastrotomy can detect the hardened, indurated irregular outlines of the ulcer. The recognition of malignant degeneration is of vital importance to a surgeon who considers a gastro-enterostomy sufficient for a stenosing prepyloric ulcer, in order not to leave behind an operable cancer. It is also important for the surgeon who favours routine resection of gastric ulcer to recognize malignant degeneration, in order to decide upon the type of resection to be done. Whereas, with a penetrating ulcer the greater omentum is left undisturbed, and the ulcer separated from the pancreas leaving the base behind; with carcinoma it becomes necessary for a radical operation not only to remove the greater omentum but also to excise the base of the ulcer from the pancreas down to healthy pancreatic tissue. This procedure raises the operative mortality rate because of the incidence of acute pancreatitis. For this reason those penetrating ulcers in which malignant degeneration is recognized at the time of the operation are usually considered inoperable.

However, in very early malignant degeneration one can still achieve a permanent cure with a typical resection for a callous ulcer leaving behind the base of the ulcer. The following illustrates such a case.

A 49-year-old innkeeper had been ill for seven years with severe epigastric pain and vomiting of acid secretions. One year ago a penetrating ulcer with a large niche was found; whereupon I advised operation but the physician disagreed. Finally, because of severe pain, loss of weight, and severe vomiting, the operation could no longer be postponed. During the night before the operation the patient had a marked gastric hæmorrhage with fainting. The operation was performed October 15, 1922, under splanchnic anæsthesia with ¼% novocain solution. An ulcer was found penetrating the lesser omentum and the pancreas, extending from the pylorus nearly to the cardia. The stomach, small and large bowel, contained much blood. Two litres of dark blood and gastric secretion were aspirated from the stomach. The pylorus was wide open, the duodenum dilated three fingerbreadths, and compressed at the ligament of Treitz by the extensive callosities of the

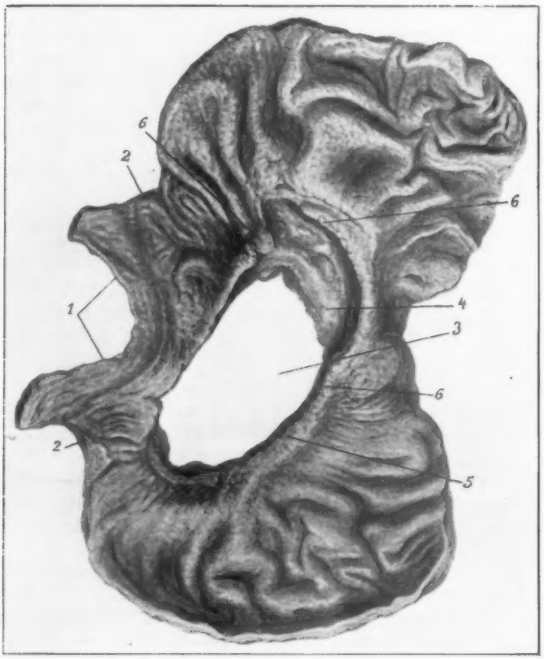

FIG. 2.—Ulcer-carcinoma specimen cut open on the curvature. 1, Duodenum, greatly dilated. 2, Pylorus. 3, Opening corresponding to ulcer base formed by the pancreas left in situ. 4, Ulcer base formed by the lesser omentum. 5, Margin of ulcer not degenerated. 6, Malignant degenerated border of the ulcer. (*Arch. für klin. Chir.*, 1924, **131**, *p.* 78. *By permission.*)

ulcer. A subtotal resection was done, leaving behind the base of the ulcer in the pancreas, which measured 8 by 3 by 1 cm. and was directly over the splenic artery. The resection extended to the right wall of the œsophagus, and the suture line of the œsophagus was covered with the fundus; end-to-side anastomosis was done according to Hofmeister-Finsterer, and the abdomen drained. Uneventful recovery. Rapid gain in weight (30 kilos). The patient is now 65 years old, completely free from symptoms, eating and drinking everything. The operative specimen showed on the lesser curvature a large defect, the former ulcer base, which measured 7 by 3 cm. Histological examination by Prof. Stoerk showed in three points of an otherwise typical callous ulcer very early tubular carcinoma, which was confined to the mucosa and submucosa. That part of the lesser omentum which had become part of the base of the ulcer was free from cancer.

Because the researches of Prof. Stoerk showed that malignant degeneration always starts at the edge of the ulcer, and that the carcinoma spreads out through the submucosa and muscularis, so that the cicatricial ulcer base remains free from infiltration for the longest time, it is reasonable to conclude that one can achieve a permanent cure even if the base of the ulcer is left behind. Therefore, in the interest of the patient, if there is malignant degeneration, and a radical operation with excision of the base of the ulcer from the pancreas is impossible, then one should perform the typical resection as with the ordinary penetrating ulcer, leaving behind the base of the ulcer instead of contenting oneself with a gastro-enterostomy in an inoperable case. With gastro-enterostomy if the ulcer has not yet degenerated, it may still do

so and there is also the possible development of a gastrojejunal ulcer. Of 226 radical operations for gastrojejunal ulcer I have three patients who had been judged inoperable by other surgeons for cancer but upon whom a gastro-enterostomy was performed to relieve the pyloric stenosis. When I reoperated the old gastric ulcer was healed but a large gastrojejunal ulcer had developed, which was removed by radical resection.

Orator determined from statistics of Haberer's Clinic that the prepyloric ulcer had a special predilection for the development of malignant degeneration (in 30% of his cases) as compared with ulcer in the pars media which occurred much more frequently but which showed an incidence of but 2% of malignant degeneration. This fact is very important when determining the management of prepyloric ulcer, but does not permit the conclusion which has been stated so often that an ulcer in the cardiac end will not become malignant. That these cases cannot be found in statistics of ulcer-cancer is explained by the fact that they are mostly regarded as inoperable if they develop in an ulcer penetrating into the pancreas. I have records of 15 such cases of ulcer-carcinoma which could not be resected.

If there is a suspicion of malignant degeneration, then the early radical operation is indicated. In such cases I perform a subtotal gastrectomy also removing the greater omentum. Whereas in cases operated upon with a diagnosis of gastric ulcer, the greater omentum and the base of the ulcer in the pancreas are left undisturbed, in cases where early malignant degeneration is recognized, not only the greater omentum but also a portion of the pancreas or liver are resected.

TABLE III.—MORTALITY OF RESECTION FOR ULCER-CARCINOMA.

Operation	Number	Deaths
Gastrectomy	.. 99	4 = 4%
Gastrectomy and resection of pancreas, liver, or colon	.. 42	14 = 33·3%
Total	.. 141	18 = 12·7%

Simple gastric resection had a mortality of 4% (99 cases with four deaths). Two of these four cases died with peritonitis without, however, leakage from line of sutures (both patients were operated during the War when asepsis was difficult to secure), and two died from pulmonary embolism. When, in addition to subtotal gastric resection, it became necessary to resect parts of the pancreas, liver, or colon, then the mortality rate increased to 33·3% (42 cases with 14 deaths). Because of the high mortality, these extensive operations are only rarely performed. As I have a number of permanent cures after such operation for malignant degeneration as well as for primary cancer, I believe it justifiable to attempt such radical surgery.

The permanent results achieved with radical operation for ulcer carcinoma are important. I have repeatedly asserted that permanent cure occurs less frequently after ulcer-carcinoma than after primary carcinoma.

TABLE IV.—END-RESULTS WITH CASES OPERATED ON 1910 TO 1933.

(*a*) *Ulcer-cancer.*

Malignant degeneration found	Number	5 years cured	
(1) Only by histological examination	35	18 = 51·4%	
(2) During the operation and histological examination	27	4 = 14·8%	9·3%
(3) Only clinically and macroscopically	37	2 = 5·4%	
Total ..	99	24 = 24·2%	

(*b*) *Primary cancer.*

	Number	Permanently cured
Gastric resection	187	58 = 31%
Gastric and pancreas-, liver- or colon-resection ..	73	19 = 26%
Total ..	260	77 = 29·6%

Groups II and III were operated on for malignant degeneration. Despite the fact that the operation was as radical as for primary cancer, the difference in permanent cures is striking when one compares 9·3% with 29·6% in primary cancer. In those patients in Group I, in whom the diagnosis of cancer was established first by histological examination, a typical resection for ulcer was done, that is removing almost entirely the lesser curvature but not disturbing the greater omentum. That the greater omentum can be the site of recurrence was demonstrated in two such patients by relaparotomy. It is perhaps of importance to note that in Group I the ulcer-carcinoma was of the infiltrating type, operations for which—when it is found in cases of primary cancer—also give poorer results than those for the cauliflower type which is usually a highly differentiated adenocarcinoma. Besides this the lymph-glands are involved earlier and more extensively in malignant degeneration than in primary carcinoma.

In 260 cases of resections for primary cancer, a five-year cure was obtained in 77=29·6%. It is interesting that also in complicated resections (including portions of pancreas, liver, or colon), 26% were alive and well after five years.

The poor prognosis of ulcer carcinoma has been reported by different authors. In 1928 Hayen mentioned that already in 1901 he had noted that prognosis of carcinoma with free HCl is worse than the prognosis of carcinoma with anacidity. Hartman made a similar observation at the Mayo Clinic for, of 41 resections performed on patients with free HCl, only 22% were alive after five years, while of 39 without free HCl 45% were alive. At the same time he noted that free HCl was present, especially in cases of prepyloric ulcer cancer. Oppolzer, of the Ranzi Clinic, found no difference in the permanent results between ulcer-carcinoma and primary carcinoma. Oppolzer believes that in my cases also there would be no difference if I would subtract those cases included in Group III in whom the diagnosis of ulcer-carcinoma could no longer be substantiated by histological examination and would include these in the list of primary carcinomas. It is open to discussion whether one should include in the group of ulcer-carcinoma or primary cancer those cases in which the history, the repeated radiological demonstration of a niche, the clinical course, and especially the macroscopic finding of radiating folds in the mucous membrane, all indicate cancer originating from an ulcer even though the histological examination can no longer show an ulcer. One can completely exclude the doubtful cases of this group, but neither should they be included in the group of primary carcinoma, as Oppolzer suggested, in order to show that in my cases also there is no difference in the prognosis. Even when excluding Group III, the cases in Group II show only 14·8% permanent cure as compared to 29·6% in primary carcinoma.

Group I, in cases of ulcer-carcinoma, operated on with the clinical diagnosis of gastric ulcer where histological examination revealed the diagnosis of early cancer, the earliest operation for carcinoma was performed. But even of these, 50% died with recurrence of the malignancy, where one would otherwise expect at least 80% permanent cures.

Bloomfield, of the Mayo Clinic, described 68 cases of ulcer-carcinoma, in which the diagnosis could only be established histologically, 36 cases, or 52·7% of which died with recurrence. The very important fact that 50% of beginning ulcer-carcinomas that were never recognized clinically but were invariably operated upon for ulcer, died of recurrence, forces us to conclude that callous gastric ulcers should be

resected before malignant degeneration starts, especially if the patient be a member of a " cancer family ".

In 1927 Chamberlain showed from the statistics of the Moynihan Clinic that with conservative management of gastric ulcer 9·5% died later with carcinoma, while the mortality rate with gastric resection for ulcer in the last few years was only 3%. He correctly concludes that gastric ulcers should be operated on early in order to prevent malignant degeneration.

It has been maintained that early diagnosis of cancer is necessary in order to improve the results of gastric resection for cancer. Naturally early diagnosis would be very valuable, but the *Proceedings* of the International Congress of Gastro-enterologists in Paris in 1937 showed that we still have a long way to go to achieve this. This holds true not only for primary cancer but even more so for early malignant degeneration. An improvement in our operative results and permanent cures can only be attained by convincing our physicians that (1) in doubtful cases an exploratory laparotomy with gastrotomy and palpation with the examining finger should be employed as a final diagnostic procedure, instead of waiting until a positive clinical diagnosis can be made, and (2) that a gastric ulcer that fails to disappear or recurs quickly after thorough and exact medical treatment should be operated upon as soon as possible, at latest within six months. The operative measure should be extensive resection not only of the ulcer but also of the chronically inflamed mucosa, especially that of the antrum which, according to Konjetzny, has a special predilection for carcinoma.

As according to Walton 20% of gastric carcinomas originate from ulcer, and as according to Hurst 16,000 in England die yearly with gastric carcinoma, the early operation for gastric ulcer could reduce the number of deaths from gastric carcinoma by 3,200 per annum. This is something that cannot be accomplished by improvement in operative technique alone, but through active collaboration between physicians and surgeons.

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Section of Laryngology

President—C. A. Scott Ridout, M.S.

[*November* 4, 1938]

Latent Nasopharyngeal Infections and Pathology of the Central and Peripheral Nervous Systems

By Georges Gibier-Rambaud (Paris)

This work is based on the following convictions: (1) That various ailments and diseases of the central and peripheral nervous systems are caused by some latent infection remaining ignored or undiagnosed; (2) that the primary foci are usually to be found in the teeth, tonsils, nasopharynx, and paranasal sinuses; (3) the value of vaccine therapy, such treatment reinforcing the resistance of the system and preventing the formation of metastases.

Vaccine therapy merely utilizes the allergic state progressively created by the infection in order to bring about the proper state of defence, and it is only in proportion with this acquired condition that the method can succeed. The peculiar susceptibility of the patient must always be tested in order to establish the proper dosage of the antigen to be administered, i.e. the vaccine. This is done by injecting a small dose intradermally and noting the local reaction. If this precaution is neglected, the treatment may be dangerous or inefficient: inefficient when too small doses are injected—the antigen acting insufficiently; dangerous because too-large doses may cause alarming general symptoms and, sometimes, local reactions followed by necrosis.

I have, within the last few years, as collaborator of my friend, Professor Laignel-Lavastine, in the neurological department of l'Hôpital de la Pitié, Paris, devoted most of my research work to troubles of the general nervous system. Permit me to cite briefly four typical cases so as to illustrate how I came to certain deductions.

A woman aged 45, affected with persistent, almost continuous, cephalalgia and vertigo for twelve years, mostly spent in various hospitals. Four months after the extraction of a number of infected teeth and treatment with an autogenous vaccine prepared with the several germs isolated from the dental apices, the patient was well and left the hospital. She had a relapse seven months later, coinciding with an acute tonsillitis. The tonsils were removed, a new vaccine was prepared and administered for three months, at the end of which the patient was perfectly well and able to resume work, for the first time in thirteen years.

A man aged 40 had been affected with auriculo-temporal neuritis for one month. Could not open his mouth and suffered excruciating pains. Three days after the extraction of a lower molar tooth with a large granuloma attached to one of the roots, the patient could begin to open his mouth, the pains were almost gone, and at the end of one week he was cured.

A woman aged 46 had been suffering from facial neuritis for three months; had ptosis of the right upper eyelid, diplopia, and intense lachrymation of the right eye. Radiographs showed that she had a subacute posterior ethmoidal and sphenoidal sinusitis. She began to improve after a few local treatments of the sinuses by replacement, and was completely cured in two months.

A man aged 36, affected with spasmodic wry-neck for nearly two years, with torsion towards the right side, had also had numerous periods of brachial neuritis for twelve years, following several attacks of grippe and tonsillitis. The patient had chronic antral sinusitis, especially of the right

side. After the surgical treatment of the antra, extraction of an infected upper molar, replacements and autogenous vaccine for several months, the patient made a complete recovery.

As far as I know, this is the first case of spasmodic wry-neck which has ever been cured. Two more cases are under treatment, one of them being almost well and the other on the road to recovery.

Other forms of neuritis, articular and muscular rheumatism, traceable to microbic infection or intoxication, and infections of the gall-bladder or prostate, may be considered as metastases of the primary foci already mentioned.

Thus a number of cases of affections of the central and peripheral nervous systems have been cured or arrested by starting from the same ætiological conception, following the same method, the same technique. Several of these affections had hitherto been considered as incurable.

For the past three years, radiographs of the paranasal sinuses have been taken in every case, according to the method of Proetz, because it is often difficult to diagnose chronic sinusitis by transillumination or by ordinary radiographs. In all my cases, the presence of a single focus of infection has been rare ; there have generally been several, and all were not always discovered at the first examination. The elimination of one focus is usually followed by amelioration, sometimes even by the total disappearance of the symptoms. These reappear after a few weeks or a few months, and there is a relapse. The elimination of a second focus is followed by the same happy but temporary result. It is only after the total elimination of all the foci of infection that complete recovery ensues.

There is another unfailing guide which indicates the presence of a neglected focus : that is the specific reaction following the injections of autogenous vaccine. This never occurs after an injection of the same dose of a heterogenous vaccine ; it is an exacerbation of the symptoms of the disease, even without febrile reaction. When this reaction manifests itself after a certain number of injections and it is impossible to increase the dose of vaccine, a closed focus remains. This was striking in one case of dementia præcox in a man now aged 30, whose disease had begun thirteen years before the beginning of treatment, two years ago. He had been operated on a few years before for frontal and antral sinusitis. New radiographs showed chronic posterior and sphenoidal sinusitis on both sides. One of the sphenoidals was punctured after antisepsis of the nares, and a few c.c. of normal saline solution were injected and withdrawn. Culture of this was negative. But the culture of a bit of the anterior wall of the same sinus (bone, submucosa, and mucosa) yielded a hæmolytic streptococcus. Previous experience had taught me that in chronic sinusitis germs are rarely on the surface of the mucosa, but in or beneath the submucosa. It was impossible to attain the maximum dose of vaccine—each attempt at increasing the dose brought on a mental reaction. Nevertheless, the incomplete vaccine course and an appropriate endocrine treatment had resulted in great improvement. Dr. Chaussé took stereoradiographs of the sphenoidal region ; there were abnormal cells extending into the great wings of the sphenoid and the pterygoid processes. On the right side these cells did not evacuate the lipiodol for several days. A radical operation was performed, opening up and draining all the sinuses, frontals excepted, at the same time. The abnormal cell was curetted—a culture of its mucosa, submucosa included, allowed the isolation of a diplococcus and a strict anaerobe, *Veillonella alcalescens*, probably missed at the time of the first culture. After the operation and vaccine treatment the patient became normal.

In all the cases of nervous troubles investigated there was always an association of aerobic and anaerobic streptococci together with one or two of the following anaerobic, Gram-negative, cocci : *Neisseria discoides*, *Veillonella alcalescens*, *Veillonella parvula*, *Staphylococcus aerogenes*, *Staphylococcus anaerobius*. Experimentally, whereas one streptococcus alone may not be pathogenic, in association with one of these anaerobic cocci, also non-pathogenic by itself, it becomes highly pathogenic.

In the majority of cases the primary foci are situated in immediate contact with the branches of the 5th cranial nerves and in close proximity to the four cephalic sympathetic ganglia, all of which communicate with the great sympathetic system by their connexions with the superior cervical ganglia. The sympathetic and parasympathetic systems send their filaments into all our organs, into the walls of even the smallest capillaries, and irritation of the sympathetic or parasympathetic may result from a direct action of microbic toxins or from the chemical products resulting from the action of these toxins on the tissue hormones. There are at least 30 different microbes causing the formation of histamine, and the action of histamine on blood-vessels is familiar. Traces of histamine have even been found in the venous blood of a muscle in activity. Many experiments have been made within the last few years upon the action of certain strictly localized stimuli, electric or chemical, applied in infinitesimal doses on certain parts of the sympathetic system, especially the solar plexus, which is easier of access and study in small laboratory animals. They all show definite effects on the capillary circulation, even in remote parts. Thus a dose of 1/2,000 of 1 c.c. (1/100 of a drop) of diphtheritic toxin injected in the vicinity of the splanchnic nerve of a guinea-pig, causes the death of the animal in two days ; 1 mgm. (1/60 gr.) of nicotine deposited near the splanchnic kills the animal in two hours ; the perisplanchnic injection of 2 mgm. of lead acetate causes its death in a few hours. The lesions found at the autopsy are multiple areas of hæmorrhagic necrosis on the surface of the stomach and the colon. Histologically, these lesions show œdema, necrosis, infiltration by leucocytes, and vascular changes of varying intensity, even thrombosis. It is possible to cause similar disorders by depositing toxic products on the latero-cervical chain of sympathetic ganglia. On the other hand, F. A. Pickworth, of the University of Birmingham, thanks to his method of staining the arterioles and fine capillaries of the brain, has shown disturbances of the cerebral circulation in pathological cases. These circulatory troubles cause zones of ischæmia and anoxæmia in various parts of the brain, the syndromes produced varying according to their anatomical localization and the multiplicity of the regions affected.

To sum up, we have been able to establish a relation between dental, naso-pharyngeal and sinus infections, and a relatively large number of affections of the central and peripheral nervous systems. The elimination of the infections and a treatment with autogenous vaccine cured the great majority of the cases treated, including syndromes heretofore considered as incurable, such as spasmodic wry-neck and dementia præcox. In some cases, treatment with endocrine extracts was employed when endocrine imbalance, which always exists in mental cases, still persisted.

It seems that the common factor that causes the various diseases is a disorder of circulation. This may be affected : (1) By a direct action of the microbes on the vascular walls causing thromboses, this being rather rare except in advanced cases ; (2) by a direct action of the metabolic products formed between microbic toxins and tissue hormones on the vascular endothelium and walls ; (3) through an irritation of the sympathetic and parasympathetic systems by direct action of the microbic toxins and by the chemical products resulting from the action of the toxins on the tissue hormones.

Discussion.—Bedford Russell said he had had an opportunity of seeing some of Dr. Rambaud's work during the past two years. He remembered an early case of vaccine treatment for which he himself had been responsible. He had injected a man against boils, and the following day there was not a square inch of the man's skin that was not studded with boils. He felt he must have omitted some step in treatment. He had certainly been greatly impressed with the successful results of the care exercised by Dr. Rambaud.

He had seen the treatment by Dr. Rambaud of two cases of dementia præcox, in both of which the results were brilliantly successful. He had also been much interested in the cultures obtained by subepithelial examination in the sinuses. It must not be thought that there was no infection

merely because a sinus had been washed out and nothing could be grown from the fluid. Some of Dr. Rambaud's work in that connexion had been confirmed by workers at St. Bartholomew's Hospital, where specimens of mucosa were steeped in 1% perchloride of mercury for half an hour so as to sterilize the surface. They then obtained a copious growth of hæmolytic streptococci in one case, in one case pneumococci, and in another case *Streptococcus viridans*.

Another feature of the method adopted by Dr. Rambaud was that there was, in inoculated cases, the most remarkable freedom from the post-operative symptoms, otherwise to be expected.

Dr. RAMBAUD (in reply) explained that, at the beginning of his research work, he had proceeded slowly—hence the rather long duration of the treatment, one cause only being dealt with at a time. Thus, in the case of spasmodic wry-neck briefly cited, intrabuccal radiographs taken to ascertain the presence of dental apical infections had shown him that the patient had right antral sinusitis. His colleagues disagreed, maintaining that he could not diagnose chronic antral sinusitis from such a radiograph. Upon his insistence, a puncture of the antrum was made ; about 3 c.c. of fairly clear mucopus was withdrawn ; it yielded a pure culture of pneumococcus. Lipiodol was introduced into the sinus while the canula was in place and radiographs made within a few minutes, with intrabuccal films, showed marked thickening of the mucosa. An improvement in the condition of the patient followed this minor intervention. An autogenous vaccine made with the pneumococcus while giving, at first, the specific reaction on which he laid stress in his paper, and bringing about some additional improvement, did not prove to be completely efficacious. Then he took radiographs of all the sinuses, according to the method of Proetz, and it was found that the left antrum was also affected, though to a lesser extent. A permanent opening into the right antrum was made and cultures of pieces of the whole thickness of the mucous lining yielded other germs, including a *Streptococcus viridans*. However, it was not until a permanent opening of the left antrum was made, followed by local treatment consisting of replacements at first with ephedrin solution and, later, with special horse serum (hemostyl), that the patient finally was completely cured.

In the last case treated, one of dementia præcox with beginning spasmodic wry-neck, within six weeks great improvement followed the extraction of impacted and infected teeth and the radical operation consisting of the opening and draining of all the sinuses, the frontals excepted. After the administration of autogenous vaccine for three months, the patient is now practically well, the vaccine treatment being continued.

Infrasellar Adamantinoma

By Major W. A. D. DRUMMOND, R.A.M.C.

ADAMANTINOMATA (ameloblastomata) are tumours which arise from remnants of the enamel organ forming embryonic epithelium.

Histologically, they may show all variations between the stratified squamous cell and the specialized ameloblast, thus demonstrating the normal course of development of the enamel organ. It is, however, doubtful if true enamel formation ever occurs.

In whatever region adamantinomata occur, they exhibit the characteristic features of the enamel organ :—

(1) A peripheral layer of epithelium corresponding to the layer of adamantoblasts of the enamel, arranged as a single palisade.

(2) A subcolumnar layer of vesicular cells analogous to the reticulated hydropic cells.

(3) A central zone of stellate cells representing the enamel pulp.

The earliest growths are solid ; later they may become cystic and attain a large size, one described by Ewing (1928) from the upper jaw being as large as a child's head.

There are three main sites of origin of these tumours, namely :—

(1) *The maxillary.*—The lower jaw is the most frequent site of occurrence, and here they tend to be of the cystic type. Those of the upper jaw are more often solid, and are usually diagnosed as multilocular cystic odontomes.

(2) *Pituitary or suprasellar.*—Critchley and Ironside (1926) have surveyed the tumours in the pituitary region and describe them as arising in unobliterated portions of the fœtal craniopharyngeal duct. Erdheim (1904) has recorded the frequent occurrence of groups of epithelial cells in the neighbourhood of the infundibulum, and these he regarded as remains of oral ectoderm, capable of giving rise to tumours. Atwell (1926), on the other hand, is of the opinion that adamantinomata arise in the pars tuberalis of the pituitary from dental elements which have become included in the anlage of the tuberal process, at the time when the pituitary was in close relation to the dental ridge.

(3) *Tibial.*—It is difficult to give an adequate explanation of the origin of these rests.

In his embryological studies, Frazer (1931) has shown that the growth of paraxial mesoderm forming the basal bars of the sphenoid constricts Rathke's pouch and so forms its neck.

The part of the neck which lies between the basis cranii and the roof of the mouth, is then caught by the developing septal processes of maxillary mesoderm and is carried for some distance along the roof, to terminate at a point on the back of the developing nasal septum immediately above the angle of junction with the soft palate. The neck is thus drawn out into a strand of cells which usually disappears by the ninth week of fœtal life. Some epithelial remnants, however, usually persist.

Haberfeld (1909) reports the regular finding of a strand of cells in the pharyngeal submucosa just behind the alæ of the vomer.

A case of persistence of the craniopharyngeal canal has been described by Cave (1931). It extended for a distance of 16 mm. downwards and forwards through the median septum of the sphenoidal sinus to a termination in the nasal septum.

He states that in only 0·20% of human skulls does the genuine canal persist in the adult (fig. 1).

In the case described below, the tumour arose in the body of the sphenoid and nasal septum, i.e. in the track of the canal (fig. 2).

A. B., a Parsee girl, aged 14 years.

Catamenia commenced September 1937, and was regular until the operation, May 1938. It then ceased until September 1938.

1931 : She was apparently a normal child up to the age of 7. During her 8th year it was noticed that she was speaking with a nasal intonation. She was complaining of headaches, which occurred two or three times a month. These were thought to be due to eye-strain, but the provision of glasses did not ameliorate the symptoms.

1932 : The child was losing weight and becoming listless. In February an acute suppurative otitis media (right) developed. The nasal speech was now more marked, and breathing was almost entirely by the mouth.

1933 : In October the tonsils and adenoids were removed in order to relieve these symptoms, but no improvement in the speech or breathing resulted. The father reports that some difficulty was experienced in removing the adenoids.

1934 : In the early part of the year febrile attacks developed and increased in duration from two to thirty days. The cause of these attacks was not diagnosed. In December she failed so hopelessly in a school examination that medical advice was again sought. It was found that the left eye could only perceive light ; a week later this eye was blind.

1935 : In March the child was still complaining of attacks of fever and the headaches had increased in severity. Later, pains developed in the back and shoulders and the neck became stiff. During an attack of intermittent pyrexia which came on in July, the temperature rose to 105° F. The condition was diagnosed as one of caries of the 1st and 2nd cervical vertebræ. An operation was performed and she was placed in a plaster of Paris jacket in which she remained until, after four months, the development of pressure sores necessitated its removal.

1936 : In January nasal obstruction was complete. A general anæsthetic was given, and it was found that the obstruction was due to a tumour. Later the child was sent to an institution

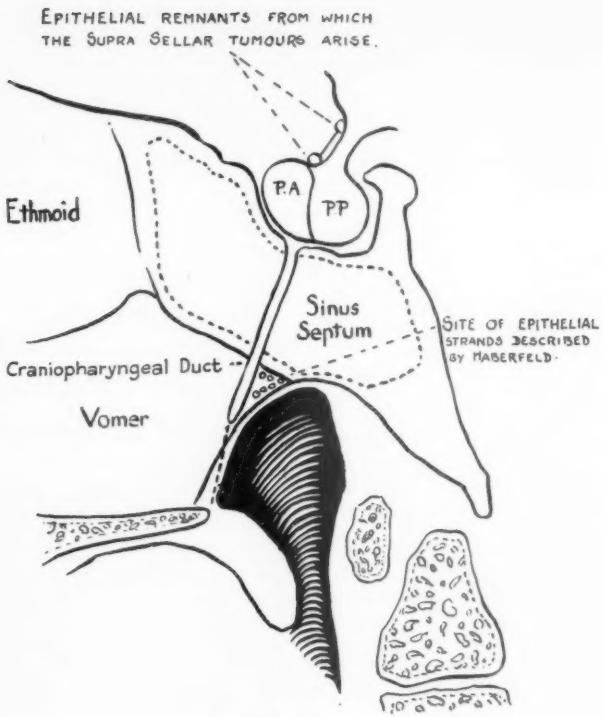

FIG. 1.

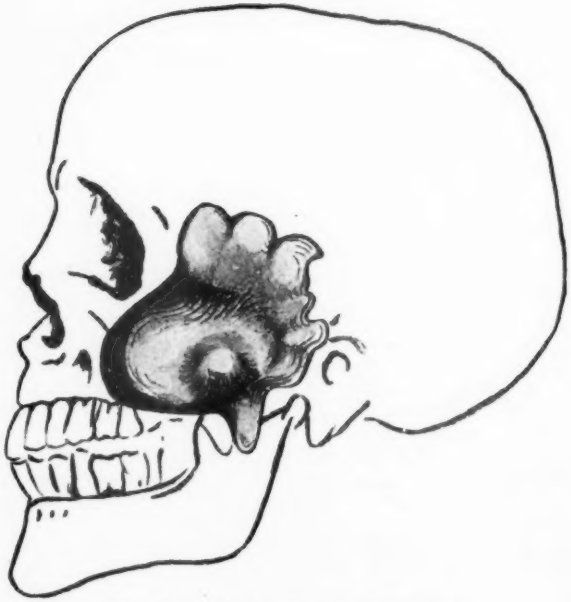

FIG. 2.—Reconstruction of the tumour

for radium therapy and, on two occasions, radium needles were inserted into the nostrils for a period of twenty-four hours. After this treatment she became very deaf.

1937 : In October she complained of pains in the throat and difficulty in swallowing, and it was found that the tumour had depressed both the hard and soft palates and was extending into the pharynx. Two further applications of radium, each lasting for eight hours, were then given.

1938 : In April it was realized that the sight of the right eye was rapidly deteriorating. Headaches were continuous and intense. There were frequent attacks of vomiting without apparent cause.

Condition on examination (23.4.38).—Patient is a frail child with a vacant expression. Both eyes are protuberant. She is listless, yawns frequently, and complains of severe headache.

Nose : In the left nasal fossa there is a red tumour extending forwards to within ¾ in. of the vestibule. Laterally, the tumour displaces the inferior turbinate and the lower half of the middle turbinate. From here it sweeps over to become confluent with the nasal septum. On the right side the growth can be seen but, owing to septal deviation, its size cannot be estimated.

Mouth : The posterior three-quarters of the hard palate and the soft palate are flattened. Posterior to the soft palate there is a grey corrugated tumour extending down into the pharynx (fig. 3).

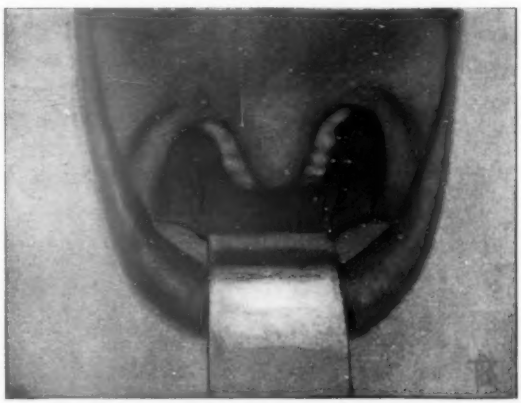

FIG. 3.

Ears : There is obstructive deafness in both ears. A large central perforation is present in the right tympanic membrane.

Blood : The Wassermann and Kahn reactions are negative.

Ophthalmological report, 26.4.38 (Lieut.-Col. J. Biggam, R.A.M.C.) : Left eye blind, right eye approximately normal. Left eye : Complete primary optic atrophy. No other fundus abnormality. Right eye : Vision $\frac{6}{12}$ with a −1·75 cylinder at 90°, reads J 6 near vision. Right fundus is normal to ophthalmoscopic examination. Visual acuity suggests early nerve involvement but no ophthalmoscopic signs of it present yet.

X-ray report, 18.5.38 (Major J. C. Coutts, R.A.M.C.) : " The central portion of the sphenoid, and the apices of the petrous bones have disappeared. The two sides are joined superiorly by a thin bony arch, the raised roof of the sphenoidal sinus.

The lateral view shows extensive bone destruction involving the sphenoid and basisphenoid with enlargement of the sphenoidal sinus which contains irregularly distributed opaque material forming poorly defined cystic spaces. The region of the sella turcica has been pushed upwards and flattened " (fig. 4).

It was considered that if no operative procedure were undertaken, death would result in the near future. It was decided to operate via the nasal route and endeavour, in the first instance,

to mobilize that part of the tumour which was distending the sphenoidal sinus and later, to remove the growth through the nasopharynx.

Operation (22.5.38). — Under morphine and local anæsthesia a submucous resection was performed and the septal cartilage removed as far as the front of the tumour. The right middle turbinate bone was then excised. This afforded room to strip the mucosa from the anterior surface of the body of the sphenoid. It was found that most of the bone had been destroyed and its place taken by a large, grey mass which transmitted the arterial pulse. An attempt was made by blunt dissection to shell out this mass from the body of the sphenoid. During this procedure it was accidentally punctured and a quantity of clear fluid was expelled in gushes. The puncture was enlarged, and a big cyst lined by white epithelium was exposed. Trabecula, formed by deposits of white crystals, adhered to the posterior wall. The cyst was explored by the finger, and on either side the internal carotid artery could be felt. While the right side was being palpated the patient complained of sharp pain and flashes of light in the right eye (fig. 5).

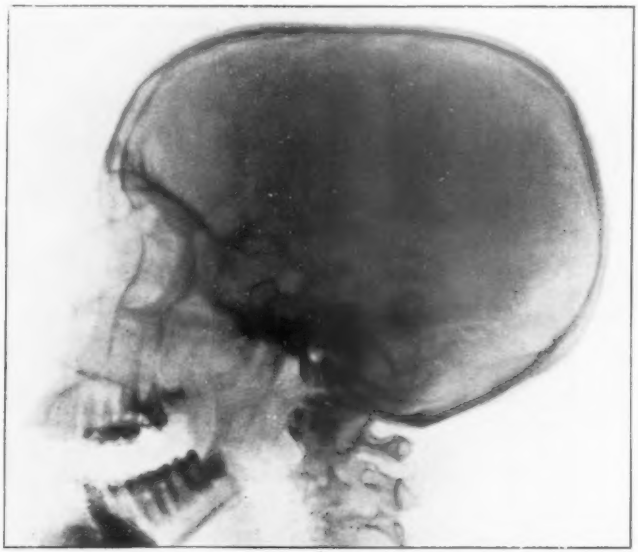

FIG. 4.—Radiograph of skull showing extensive destruction of the sphenoid and basi-sphenoid.

After the operation the temperature rose to 104° F. and fell to normal by the fifth day. During this time the patient complained of periodic dimness of vision. A week later there was a transient rise of temperature which subsided after two days.

Headaches and vomiting had now entirely ceased. The child was no longer sleepy and she began to take an intelligent interest in life.

26.6.38 : The patient complained of a right-sided neuralgia and a thick white discharge from the right nostril. The right antrum was washed out and a large quantity of old blood-clot and mucus removed. After this the temperature rose to 103° F., and the febrile attack lasted for six days.

Second operation (14.7.38).—A horizontal incision was made through the nasal septum on the level of the floor of the nasal fossa up to the edge of the tumour and the septum dislocated to the right. The septum was then incised round and over the tumour, the incision being carried postero-superiorly to the cribriform plate. Inferiorly, incisions were made through the mucosa of the floor of the nose anterior and lateral to the tumour and then, by blunt dissection, an

endeavour was made to roll the growth through the nasopharynx. This was found to be impossible owing to its deep extensions into the soft palate and basisphenoid, and it had eventually to be removed piecemeal. The basisphenoid with the anterior half of the margin of the foramen magnum and part of the anterior arch of the atlas had to be removed in the extirpation of the nasopharyngeal mass. The pharyngeal orifices of the Eustachian tubes were completely blocked by lateral extensions of the tumour. Although the tumour had infiltrated the body of the sphenoid, the basisphenoid, the nasal septum, and the soft palate, it had not invaded the lateral nasal walls, despite the fact that they were distorted by pressure.

After extirpation of the tumour there was a febrile attack during which the temperature rose to 104° F. This attack lasted for five days and loss of vision was again noted.

Cases of adamantinomata quoted in the literature have shown rise in temperature after operation. This rise was thought to be due to the liberation of toxic material during the removal of the tumour, but more probably results from injury to the hypothalamic region.

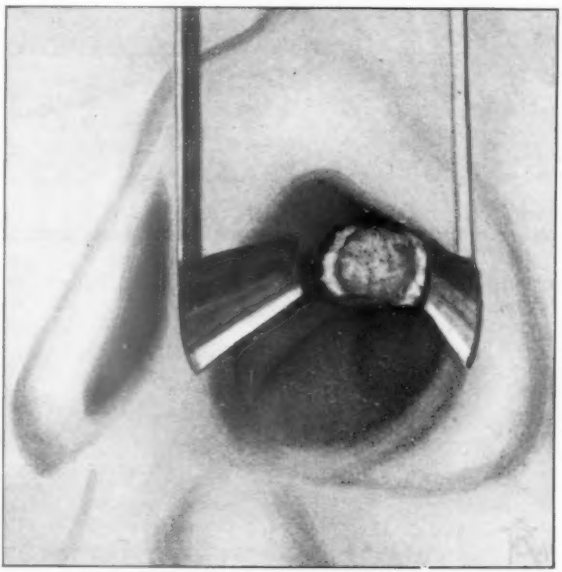

FIG. 5.—Showing the appearance of the tumour after the mucosa had been stripped from the body of the sphenoid and the cartilaginous part of the septum removed. Note the sphenoidal and maxillary divisions of the tumour.

Pathological report, 2.8.38 (Major H. J. Bensted, R.A.M.C.): This is an epithelial tumour that consists for the most part of a cystic-adenomatous structure. The epithelium lining the cysts varies from the high to the flattened type. In many cases there are papillomatous projections of the wall into the cyst cavity.

The general structure is suggestive of an adamantinoma of the so-called glandular type (figs. 6 and 7).

Second ophthalmological report: Distant vision. Right eye $\frac{6}{12}$ with glasses. Reads near Jaeger 1 with difficulty.

The right optic disc shows a primary optic atrophy. It is abnormally pale and the lamina cribrosa shows well. The ophthalmoscopic signs are now apparent.

Progress.—Report, 27.10.38: The child is in good health. She has put on weight and now takes an active part in games. There have been no recurrences of headache since the first operation. Breathing is now nasal. There is no further improvement in the vision of the right eye.

FIG. 6.—Section showing glandular type of structure, together with many small cystic spaces (× 15).

FIG. 7.—Section showing solid portion of tumour (× 20).

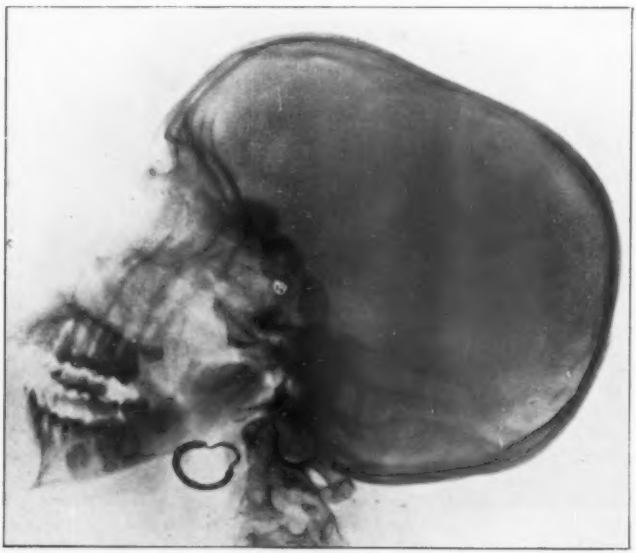

FIG. 8.—Radiograph of skull three months after operation, showing considerable thickening of the bony arch joining the two sides of the sphenoid. (X-ray report by Major J. C. Coutts.)

Comment

The following facts support the view that this tumour arose from the vestigial craniopharyngeal duct :—

(*a*) The presence in 0·20% of adults of a patent craniopharyngeal canal which may extend from the floor of the sella turcica through the sphenoidal septum into the vomer.

(*b*) Isolated para-dental débris or epithelial rests have constantly been found along this axis.

(*c*) The body or axis of the tumour extends from the under-surface of the floor of the sella turcica, through the sphenoidal air sinus into the vomer to terminate immediately above the junction of the soft palate and the nasal septum, i.e. it follows the course of the craniopharyngeal duct.

The tumour thus forms a link between the suprasellar and the maxillary adamantinomata.

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Tuberculosis of the Larynx.—STEPHEN SUGGIT.

Female, aged 26.

Admitted to Harefield sanatorium on October 7, 1937, with a history of huskiness, duration one year. First seen January 1938, when indirect laryngoscopy showed a pale turban-like œdema of the whole epiglottis and arytenoids, without ulceration. From then until leaving the sanatorium on July 1, 1938, the condition slowly improved. A biopsy was performed on June 21 on pieces of tissue removed from epiglottis and left arytenoid. The sections (on view for inspection) show rather atypical tuberculous granulation tissue. During the patient's stay in the sanatorium she was under the care of Dr. Stokes, who at no time found any clinical, radiological, or bacteriological evidence of tuberculosis apart from in the larynx.

Discussion.—R. SCOTT STEVENSON said he happened to have a similar case in a youth of about 19 under his care at the moment. There were no tubercle bacilli in his sputum and no clinical or X-ray evidence of tuberculosis in the lungs. It was unfortunate that such cases slipped into the literature every now and then as being cases of primary tuberculosis in the larynx. He thought that everyone now admitted that true tuberculosis of the larynx was never primary in that site. Cases such as that shown by Mr. Suggit were not strictly true tuberculosis but lupus; and that was what he took Mr. Suggit's case to be, a typical case of lupus of the larynx. His own case had been treated with a long course of direct ultra-violet light without any improvement whatever, but he was now going to carry out tracheotomy and give the larynx complete rest, which he considered beneficial in lupus though not in tuberculosis.

STCLAIR THOMSON said that the case under discussion was a manifestation of tuberculosis, but he would rather it were not called tuberculosis of the larynx. It would be better, while agreeing that pathologically it was a form of tuberculosis, to say it was either lupus or, to use a term he had coined many years ago, a "lupoid" form of tubercle of the larynx.

It was rather bold, in view of the lessons of present-day methods, to say there was "nothing in a chest". Many years ago it was stated positively that there was nothing in lots of chests where to-day the X-ray revealed that there might be extensive trouble, trouble incalculable according to the methods of investigations available in former days. He thought it possible that, though there was no evidence of it, there was likely to be undiscoverable tuberculosis in the lungs of this patient, as in the lungs of any individual suffering with lupoid disease of the larynx.

It was only necessary for the young woman to get married and have several pregnancies for the condition of the lungs to develop into tuberculosis, for her to develop subacute or even acute tuberculosis, and to die of it. Such cases should, therefore, always be treated seriously.

He had tried and seen nearly every treatment recommended in Europe. He had seen a most thorough trial of the Strandberg's method of diffused general light, the negative results of which he had published. He did not wish to say it might not be of some help to out-patients in the poorer neighbourhoods, but for those who could go to a sanatorium such general methods were of no additional use.

He had lived through the days when he had seen " active surgery " in tubercle of the larynx, and was glad to have assisted in abolishing it. The only reliable local treatment—not often indicated—was the cautery. There was no harm in using a galvano-cautery in the larynx in suitable cases, if it was used correctly. The lesion in the case under discussion was not superficial ; it was deep. The surface of the girl's larynx was intact. The galvano-cautery was not used to " burn away " the disease ; it was used to stimulate fibrosis. He would not, however, be in a hurry to use the galvano-cautery in that case because the girl was already showing improvement. There was no deep lesion of the cricoarytenoid joint, and that was important in all such cases. If the cricoarytenoid joint was invaded, as shown by impaired movement, the case had then become serious. This patient would, he thought, do very well.

No one had explained to him why lupus was almost unknown in America. He had shown cases of lupus to elderly American laryngologists visiting England and they had never previously seen a single case. It was supposed to be due to poverty and dirt. The Danes were amongst the cleanest, most intelligent, best-fed, and well-dressed and well-housed people in Europe, and yet they had abundance of lupus. In Naples people lived in the most awful dwellings and subsisted on macaroni and sunlight, and they did not know what lupus was. They got tuberculosis, but not lupus.

W. A. Mill said he had a man with a similar condition of the larynx under his care for five and a half years, and at no time had anything been found in his chest. He had some antral infection which was operated on. At operation the lining of the membrane was seen to be very much thickened and was found to be studded with tubercles. For a while the man had treatment by rest and spent a short period in Brompton Hospital. The galvano-cautery was then used. The man had had no treatment other than inhalations for about four years. His larynx was gradually getting better, and he had been at work for the last four years in a factory. He was a little husky. Nevertheless, the larynx was improving steadily all the time.

F. A. H. Simmonds, speaking as one who dealt with tuberculosis and not as a laryngologist, said there were certain points of particular interest in cases of the type shown by Mr. Suggit. He would not call it primary tuberculosis of the larynx because with the primary tuberculous lesion was always associated enlarged glands. The patient had no enlarged glands in the neck. The ordinary type of tuberculosis of the larynx seen so commonly in sanatoria might be called a tertiary lesion which was dependent on ulceration in the lung. But following primary infection with tuberculosis there was dissemination of bacilli in a post-primary stage, when lesions might occur in any part of the body. Quite commonly the lungs were involved, and only later did those lesions become phthisis. Other lesions occurred in the bones, the kidneys and so on, in the post-primary stage. It seemed to him that the larynx might also be involved in that post-primary stage of tuberculosis, and that the infection was carried to the larynx by the blood-stream, and not by the bronchial tree as in the tertiary lesion. If he might say so without appearing to speak as an authority on laryngology, the lesion in the present case had the characteristics of lupus, or was at least lupoid.

From his observation of such cases in a sanatorium they appeared to remain stationary under routine treatment without particular modification by any treatment he had adopted.

H. V. Forster said he had been much interested in Sir StClair Thomson's remarks concerning the distribution of lupus. He saw such cases occasionally in the Isle of Man, and was prepared to find this disease rather more often in the Manx than in the people of the mainland.

After hearing Dr. Simmonds' remarks he was reminded of a recent article by H. Videbech,[1] though this referred to lupus within the nose. Videbech had come to the conclusion that endonasal lupus was probably a disease of hæmatogenous origin.

[1] H. Videbech (Viborg), *Acta Oto-Laryngologica*, **25**, 463.

Section of Neurology

President—J. G. GREENFIELD, M.D.

[*November* 17, 1938]

CASES SHOWN AT THE HOSPITAL FOR EPILEPSY AND PARALYSIS, MAIDA VALE.

Simmonds' Disease (Pituitary Cachexia).—ANTHONY FEILING, M.D.

Male, aged 23. Seven years ago began to feel weak and to have attacks of nausea and vomiting with some abdominal pains and headache. Has gradually lost weight and strength. Has never attained normal sexual development, the genitalia being always small and having never had erections or emissions.

Patient is extremely emaciated and feeble. Height 5 ft. 3 in.; weight 4 st. 13 lb. Appears anæmic, with a pale skin which is thin and atrophic and tightly stretched. He has no pubic or axillary hair and has never shaved his face. The external genitalia are small, with a small penis and testicles, both of which are in the scrotum. The limbs, face, and head are of normal size compared with the body. Eyes normal; vision good; visual fields full and optic discs normal. No paralysis of any kind and no abnormal physical signs in the nervous system. Heart and lungs appear normal. Blood-pressure very low, 90/60. Pulse soft and slow, usually 60 per minute. Abdomen retracted but nothing abnormal can be palpated.

In hospital the patient is always apathetic and inclined to be drowsy. Complains of a good deal of abdominal pain and has occasionally vomited.

Investigations.—Urine: No abnormal constituents. Wassermann reaction in blood negative. Blood-count: R.B.C. 3,720,000 per c.mm.; Hb. 73%; C.I. 0·98; W.B.C. 5,360. Differential count normal. Resting blood-sugar low, 0·072%. After 50 grm. glucose figures were at ½ hour 0·074, at 1 hour 0·120, at 1½ hours 0·135, at 2 hours 0·122, at 2½ hours 0·110.

Skiagram of the skull shows perhaps a rather deep sella turcica but nothing else abnormal. Barium meal shows pronounced gastritis but no evidence of an organic lesion in the stomach or intestinal tract. A fractional test meal has shown complete achlorhydria.

The case exhibits all the principal features of this condition, the most striking points being the loss of weight and emaciation and the extraordinary degree of weakness and asthenia. I should like to draw attention to the fact that there are no signs or symptoms to indicate gross tumour of the pituitary body in the shape of failure of vision, alterations in the visual fields, or changes in the optic disc. The patient has occasional headaches and vomiting, but I am quite satisfied that these are not such as would be associated with increase of intracranial tension. It has been suggested by

Zondek, who has noticed the occurrence of vomiting and paroxysmal pain in these cases, that these symptoms are due to a vagotonia. We have begun to treat the patient with daily injections of prolan, and if that does not serve I am going to treat him with pure anterior pituitary substance. As far as I can make out most of these cases of genuine pituitary cachexia are due either to a necrosis of some kind of the anterior lobe of the pituitary, or atrophy, or a cystic degeneration, and therefore it is not very likely that medication would produce very good results.

Discussion.—Dr. F. PARKES WEBER suggested an alternative diagnosis, that the disease was not in the brain at all, but that this was a condition which had been described by Dr. Roger Korbsch (*Deut. Med. Woch.*, 1936, **62**, 1948) as "gastritis atrophicans juvenilis". This author had carried out repeated gastroscopic examinations by the easily passed flexible gastroscope, and he had come to the conclusion that the condition was an idiopathic atrophy of the gastric mucosa, which was apparently not fatal, and in which recovery might be attained. Such cases had been mistaken chiefly for Simmonds' disease, and one or two had been actually diagnosed as such.

POSTSCRIPT.—The present patient was, however, a male, and according to Korbsch "gastritis atrophicans juvenilis" seemed to be confined to the female sex.—F. P. W., November 23, 1938.

Dr. H. LEVY said that the condition of "gastritis atrophica juvenilis" might be due to the pituitary cachexia. An influence of the pituitary on gastric functions has been suggested by Cushing's repeated observation of acute perforating ulcers occurring a few days after operation for an anterior lobe adenoma and by the work of Dodds and his collaborators with posterior lobe extracts.

POSTSCRIPT (25.11.38).—The present case resembles in several important points those reported by I. Snapper, J. Groen, D. Hunter, and L. J. Witts (*Quart. J. Med.*, 1937, **30** (n.s.6.) 195). These authors regarded the achlorhydria of their patients as caused by the co-existing anterior pituitary deficiency.

Dr. ANTHONY FEILING (in reply to Dr. Parkes Weber) said that this patient had not been gastroscoped. Dr. Weber's remarks recalled to his mind that quite recently Dr. Sheldon, in a paper, drew attention to the fact that in his opinion a number of cases of anorexia nervosa had been mistakenly called Simmonds' syndrome. That was not the case in this patient because he did not have anorexia.

Spinal Tumour with Extreme Scoliosis.—ANTHONY FEILING, M.D.

Female, aged 53, single. It is stated that scoliosis has gradually developed since the age of 10. In 1925 the left breast was amputated because of chronic mastitis.

In 1932 attacks of profuse sweating above the waist were noticed, which came on spontaneously. In 1933 the feet and legs felt swollen, and weakness gradually appeared in both legs. A little later a slight weakness of the left hand was noticed. The weakness gradually increased so that by the present year she was just able to walk. Micturition was a little difficult, but no incontinence occurred till lately. Loss of sensation has been noticed in the legs during the past year. No severe pain of any kind.

On September 12, 1938, a lumbar puncture was performed, after which all her symptoms became considerably worse. Thus the weakness of the legs and of the left arm was increased, she became unable to walk, and bladder control was lost. Cerebrospinal fluid: Clear and bright yellow in colour; protein 1·5%. Globulin +, Wassermann reaction negative. Chlorides 745. Pressure not taken but only 6 c.c. of fluid were obtained.

Condition on admission.—A very extreme S-shaped scoliosis, the curve beginning in the upper dorsal region and extending as far as the lumbar. Cranial nerves normal except for ? some wasting of the trapezii muscles. Loss of motor power marked in

the whole of the left upper extremity, with slight general wasting of the muscles. Slight weakness of the right arm. No complete paralysis of any group of muscles. Arm-jerks : Supinators present on both sides, biceps lost, triceps obtained. Weakness of abdominal muscles on both sides with absence of all the abdominal reflexes. Legs : A gross spastic paraplegia, more marked on the left side. Frequent involuntary flexor spasms, especially of the right leg. Both knee and both ankle jerks exaggerated; double ankle clonus and double extensor plantar reflexes.

Sensation : On right side all forms of sensation grossly affected up to level of D.1. In the lower segments the loss is complete and becomes gradually less as higher segments are reached. On the left side the loss extended higher, analgesia and therm anæsthesia extending as high as C. 5 with hyperæsthesia over C. 4 and perhaps C. 3.

X-ray examination of the spine showed severe scoliosis but no other abnormality. A diagnosis of tumour of the cervical cord was made. ? intramedullary.

Operation, 12.10.38 (Mr. W. McKissock).—Laminectomy from C. 2 to C. 6. An intramedullary tumour was found extending certainly from the 2nd to the 4th segments. The cord was incised in the mid-line and a soft brownish tumour exposed which it was considered inadvisable to attempt to remove.

I show this case for the interest attaching to this combination. In some cases scoliosis does appear to be definitely connected with tumours of the spinal cord, both intra- and extra-medullary. In this case I am not suggesting that the scoliosis and the tumour are causally associated because, according to the history, the scoliosis appeared at the age of 10, whereas no symptoms that could be applicable to the spinal tumour appeared until the patient was 47. I have always myself believed that it was possible to get paraplegia simply from scoliosis, although I never knew exactly how this came about. In this case there was no doubt from the clinical examination that the lesion was high up in the cervical spinal cord, a long way above the curve in the spinal column. We thought it impossible that the two could be directly related. It is also worthy of note that the patient's symptoms were made very much worse by lumbar puncture, an effect which I have previously observed in cases of spinal cord compression. The microscopic examination of the tumour has shown it to be very cellular and of the nature of a glioma.

Discussion.—Dr. S. NEVIN said that he considered the tumour in Dr. Feiling's case to be a glioma of ependymal origin.

The PRESIDENT asked Mr. McKissock, who had performed the operation, whether he determined the question as to syringomyelia below the tumour, accounting for a possible relationship between the tumour and the scoliosis.

Mr. W. MCKISSOCK replied that he split the cord open and exposed the tumour, but did no more than that.

Dr. ANTHONY FEILING said that in 1913 a case was published by Dr. Wilfred Harris and Mr. Blundell Bankart of a woman younger than this patient. There was not such a long history of scoliosis, but it went back for four or five years, and the scoliosis was very marked with symptoms of paraplegia, the level of the tumour being obviously above the level of the scoliosis. At operation an extramedullary spinal tumour was removed. The patient recovered completely from the paraplegia, but he did not know whether she recovered from the scoliosis.

Meningioma of Occipital Lobe.—A. DICKSON WRIGHT, M.S.

Dr. McAlpine's patient, Miss F. L. P., aged 57, a masseuse, was admitted to hospital on October 12, 1937, with a history of three years of mental deterioration, head and neck ache, and loss of memory, for a lesser period of time vision had been deteriorating. On admission the patient was very peculiar in demeanour ; she was

not orientated, and seemed to be a religious dement. Examination disclosed a very slight hemiplegia of the right side and finger apraxia and agnosia of the right hand. The visual fields showed a right homonymous hemianopia with macular sparing, the retinal veins were full, and vision was poor ($\frac{6}{18}$) in both eyes.

A ventriculogram revealed the most extreme displacement affecting all the ventricles from a left occipital tumour. An operation was performed (2.9.37) under local anæsthesia, and a gigantic meningioma removed. The tumour had completely destroyed the left occipital lobe, and after removal only a translucent layer of ependyma covered the posterior part of the lateral ventricle. The tumour weighed, immediately after removal, $10\frac{3}{4}$ oz. or 300 grm. (fig. 1).

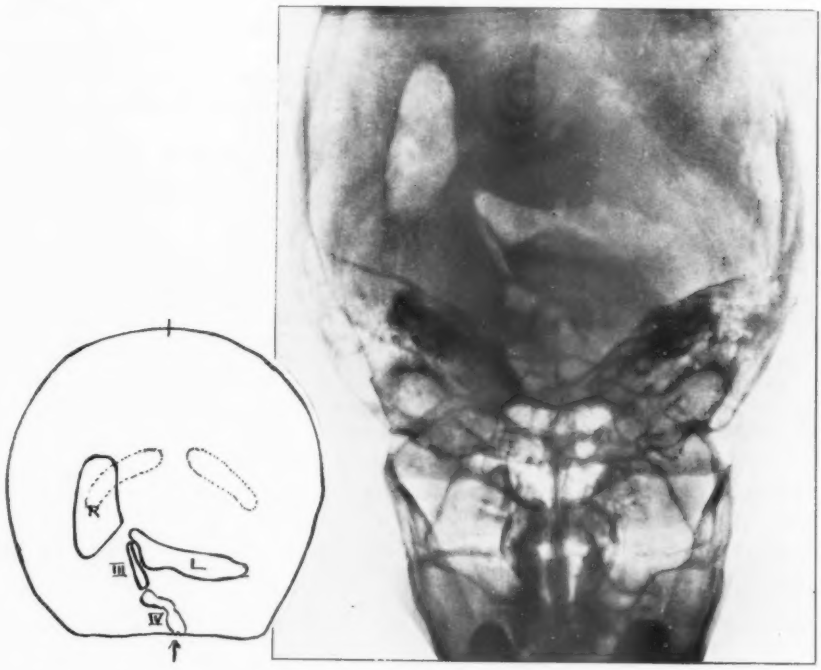

FIG. 1.—Ventriculogram showing gross displacement of whole ventricular system to the right with downward displacement of the left lateral ventricle. (Antero-posterior view.)

The patient's gradual recovery of her reason and her sight following the operation made a most fascinating clinical study, the vision becoming $\frac{6}{6}$ and the religious dementia transformed to Anglican orthodoxy. A fracture of the neck of the femur sustained in a fall out of bed the day after operation was satisfactorily treated with a Smith-Petersen pin.

The main interest of this case lies in the great size of the tumour, one-fifth of the weight of the brain. It is astonishing that the cranial cavity should be able to find space for such a large volume of growth.

Hernia Cerebri treated by Thiersch Skin Grafts.—A. DICKSON WRIGHT, M.S.

Dr. Anthony Feiling's patient, Mrs. E. W., aged 47, was admitted to hospital in April 1937 with a one year's history of headaches and progressive right-sided paralysis starting in the hand, and for the last two months aphasia had been increasing. On admission the right side was immobile, there was a partial aphasia, and she was very drowsy and disorientated.

On the diagnosis of parasagittal meningioma a large fronto-parietal flap was turned down, but after incising the dura and removing a small piece of tumour the patient's condition was so serious that the operation had to be abandoned. She was extremely ill following this operation and a putrid empyema developed which was

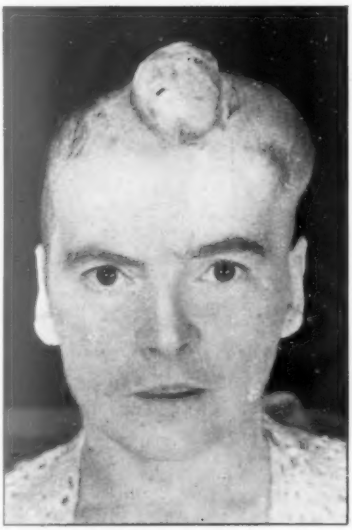

FIG. 1.—E. W., 17.8.37.

cured by repeated aspirations, and the lung abscess, the origin of the empyema, was coughed up. The head wound became badly infected and a great deal of dead bone could be seen in the wound.

The bone flap was removed three months later; by this time the patient was totally aphasic. Following this operation a huge hernia cerebri developed (fig. 1). This was covered with Thiersch grafts as suggested by Oljenick, and finally, four months after the first operation, the meningioma was removed through a straight incision, having the same relation to the skin flap as an arrow has to a bow. Following this operation the hernia receded and during the next three months her speech slowly came back to her, and the right leg regained its power, but unfortunately the right arm remains paralysed.

This method of covering a raw septic cerebral hernia seems to be of the greatest

value in preventing further infection of the hernia and also in making operative procedures possible in an uninfected field (figs. 2 and 3).

FIG. 2.—E. W., 31.3.38.

FIG. 3.—E. W., 31.3.38.

Pineal Tumour with Invasion of Quadrigeminal Plate. Unusual Type of Paresis of Reflex Ocular Movements. Treated by Subtemporal Decompression and Radiotherapy.—DOUGLAS MCALPINE, M.D., and P. B. ASCROFT, F.R.C.S.

W. L., male, aged 22. Admitted to Middlesex Hospital on March 1, 1938. At the beginning of January he had a severe headache which lasted a day. Headache recurred early in February and became increasingly severe, being referred to the frontal and occipital regions. Vomiting began about the middle of February and continued. No history of giddiness, diplopia, failure of vision, deafness, alteration in weight, or of polyuria was obtained.

The chief points on examination were: (1) Approximately 5 diopters of papillœdema with exudate and hæmorrhages around both discs; visual fields full. (2) Pupils moderate in size, regular in outline, no reaction to light but normal reaction on convergence. No ptosis or lid retraction. Ocular movements full, except that upward movement both eyes was slowed, especially to command. (3) Slight right lower facial weakness. (4) Hearing good and equal on the two sides. (5) No paresis of the limbs, alteration in the reflexes, or sensory loss. (6) Body conformation normal, including genitalia.

Blood Wassermann reaction negative. Cerebrospinal fluid: Pressure 350 mm. of water. Wassermann reaction negative. Cells, 140 lymphocytes per c.mm. Total protein 0·03%. Lange curve normal.

The signs remained unchanged until March 9 when he complained of deafness and double vision on looking upwards and to the right. No additional paresis of upward movement could be detected. Left-sided deafness was now apparent; a watch was

heard 27 in. right ear, 3 in. left ear. Rinne positive on the left side and Weber referred to the right.

Skiagram of skull: "Pineal gland heavily calcified, but not displaced. About 1 cm. behind the pineal shadow is a slightly irregular opacity, probably in the same plane."

The fixed pupils to light, the early signs of paresis of upward movement and the left-sided deafness, suggested a tumour invading the quadrigeminal plate, probably originating from the pineal gland.

14.3.38: Ventriculogram. Symmetrical internal hydrocephalus including the 3rd ventricle. The posterior part of the 3rd ventricle showed a rounded filling defect. This appearance confirmed the diagnosis of pineal tumour.

A right subtemporal decompression was performed, followed by deep X-ray treatment (37 exposures over 5 fields). This was completed by 16.5.38, with complete relief of headache and subsidence of papilloedema.

About 4.4.38 patient noticed that if he raised his head from a book, his eyes lagged behind. This was confirmed on examination, which showed that upward movement of the eyes when associated with a corresponding movement of the head, was much slower and more difficult than when carried out as a solitary act. Other reflex movements in response to a bright light or a sudden noise were equally affected. On the other hand, the patient was able to follow an object fully upwards at nearly normal rate. Turning the eyes upwards to command seemed slower. These signs have persisted. Hearing on the left side is now within normal limits. The discs are flat, but slightly pale. Vision $\frac{6}{6}$ both eyes. No hypothalamic symptoms are complained of. The patient feels quite well and is at work.

One interesting point about this case is the treatment. We took the view that as these tumours of the pineal body are very radio-sensitive a simple decompression should be followed by radiotherapy. We think that treatment has been justified.

Discussion.—Dr. PARKES WEBER asked whether it was really the rule that in pineal tumours commencing in adult life there were no sexual organ changes. In young boys with pineal tumour there was often precocious sexual and bodily development. In connexion with the question of the pineal tumour being the actual cause of the macrogenitosomia in such cases it seemed very doubtful whether the pineal tumour itself, apart from its size and position, did produce these symptoms.

Dr. MCALPINE said that in his view the supposed relationship between pineal tumours and sexual abnormalities had been overstressed. The general feeling was that it was probably involvement of the mammillary bodies that caused this sexual overdevelopment.

The PRESIDENT said that a very interesting point in the case was the high lymphocyte count (140 per c.mm.). The same thing had been found several times in true pineal tumours. He supposed it was related to the large number of lymphocytes in the tumour itself. He quite agreed with what had been said as to the overstressing of the sexual development.

Chronic External Hydrocephalus following Otitis Media and Ablation of Lateral Sinus.—DOUGLAS MCALPINE, M.D.

I. C., female, aged 17.

4.3.37: Following acute right otitis media, mastoidectomy was performed at the Western Infirmary, Glasgow. The lateral sinus, placed anteriorly, was accidentally opened and had to be packed. 8.3.37: Severe headache, vomiting, lethargy, and nystagmus to the right. Improvement until 17.3.37, when headache and vomiting returned. 24.3.37: Double vision. 26.3.37: "Pronounced papilloedema with many exudates and flame-shaped hæmorrhages" (Dr. A. J. Ballantyne). By the middle of May, double vision was no longer present and headache was slight. At

the end of March failure of vision had been noted and this was progressive. 18.5.37 : " Vision right eye, hand movements only ; left $\frac{6}{60}$. Still marked papillœdema with increase of exudate " (Dr. A. J. Ballantyne).

2.7.37 : Seen by Mr. Maurice Whiting at Middlesex Hospital. Marked bilateral papillœdema ; well-defined groups of exudate in both macular regions ; patches of woolly exudate elsewhere. Vision : Right eye, can count fingers with difficulty, left $\frac{6}{60}$.

19.7.37 : Admitted to Middlesex Hospital.

On examination.—Healthy, somewhat obese young woman, mentally alert and cheerful. Approximately 5 diopters of papillœdema and slight pallor of discs. Extensive retinal exudate, taking star shape in macular regions. Vision as on 2.7.37. Free from headache, except for an occasional period of an hour or so. No ocular paresis, nystagmus, or aural discharge. Mild degree of middle-ear deafness. Central nervous system otherwise normal except upper-limb reflexes much depressed. Cerebrospinal fluid : Pressure 300 mm. +. Queckenstedt's test negative ; cells 3 per c.mm., protein 0·03%. Wassermann reaction negative.

Skiagram of skull and sinuses : Negative, except that some mastoid cells were still apparent on right side.

23.7.37 : Ventricular tap (Mr. P. Ascroft) : Initial pressure 600 mm. +, 10 c.c. cerebrospinal fluid withdrawn ; pressure now zero.

A diagnosis of toxic hydrocephalus was made. 24 lumbar punctures were carried out between the date of admission and October 1937. During the first two months pressure was sometimes as low as 200 mm., but later the figures were in the neighbourhood of 300 mm. Amounts of cerebrospinal fluid withdrawn varied from 10 to 20 c.c., with consequent lowering of the pressure by half. During this time the patient was up and about the ward, apparently well except for a very occasional headache. The papillœdema very slowly subsided and the exudates became absorbed. Vision improved so that by October 1937, right eye could count fingers easily, left $\frac{6}{24}$.

6.10.37 : As no focus could be found in throat or nose, Mr. Hastings explored the right mastoid and removed the few remaining cells, which were healthy.

Subsequent history.—Readmission at intervals during the present year. Patient has remained well and free from headache, except on rare occasions. Cerebrospinal fluid : Pressure has varied between 220 and 300 mm.+.

15.7.38 : Ventriculogram (Mr. P. Ascroft) : Pressure left ventricle 175 mm. ; ventricles empty after withdrawal of 20 c.c. of fluid. Ventricles very slightly increased in size, but normal in shape and position.

Since July 1938 fluid restriction to 30 oz. a day and reduction of salt intake. Since then nine further lumbar punctures (no fluid withdrawn) ; definite tendency to lower figures.

9.11.38 : Patient at work for last three weeks. No headache. Vision : Right $\frac{6}{60}$, left $\frac{6}{12}$. One diopter of papillœdema left eye ; both discs show post-neuritic atrophy, right more than left. Diffuse macular changes right side. Cerebrospinal fluid : Pressure 280 ; compression of right and left jugular veins showed an equal rise on either side of approximately 45 mm., and an equal fall.

On the question of causation, obviously the simple obliteration of one lateral sinus cannot be held responsible. This brings up a point that has been raised by Dr. Symonds as to whether in some of these cases of what he calls otitic hydrocephalus, there is not a spread of infection backwards to the superior longitudinal sinus ; and it is the blockage of that sinus that is responsible for the picture of hydrocephalus. The persistence of the hydrocephalus, in the absence of a " focus ", rather favours his explanation. This patient did not present the signs one usually associates with an infection of the sinuses. We have now adopted a conservative treatment ; we do not intend to do anything more, as the patient's intracranial pressure seems to have become stabilized.

Discussion.—Dr. D. J. WILLIAMS said that in a series of papers published in *Brain* Bedford had described the results of artificial obstruction to the cerebral venous drainage in dogs. The cerebrospinal fluid pressure rose rapidly, and there was a relationship between the venous pressure and the rise in the cerebrospinal fluid pressure. As time went on the cerebrospinal fluid pressure came down to its former level. If a similar compensation took place in man it was probable that the mechanism producing a continued high intracranial pressure in these cases of hydrocephalus was not related to cerebral venous thromboses.

Dr. P. C. P. CLOAKE asked whether it was possible to decrease the output of the cerebrospinal fluid by irradiation of the choroid plexuses. He had tried this once or twice in hydrocephalus without any apparent effect.

Dr. ALEXANDER ORLEY said that they had treated at the West End Hospital cases of internal non-obstructive hydrocephalus with deep X-rays with very good results. The hydrocephalus in such cases is frequently due to hypersecretion of the choroid plexus and the X-rays have an inhibitory effect on the secretion.

Mr. G. C. KNIGHT described a patient with a large hernia cerebri, following a decompression performed at another hospital for a presumed cerebral tumour two years previously. Investigation showed that she had a closed internal hydrocephalus from arachnoiditis of the posterior fossa. She was treated with deep X-rays on two occasions, and on each occasion the hernia became flat, which was evidence he thought of the effect on the choroid plexus, although this effect only lasted for a few months. For this reason he operated subsequently, and following division of the obstructing adhesions there has been no further evidence of obstruction and hydrocephalus.

Meningitis Serosa Circumscripta Spinalis in a Boy Aged 9 Years, 10 Months.—W. G. WYLLIE, M.D.

Leslie N., first seen March 1937. Since summer 1934 walking became progressively worse and left foot dragged. For three months previously it had been noticed that he lost control of the rectum when excited, and had frequency of micturition by day and nocturnal enuresis.

On examination.—Power: Moderate weakness of both legs, left weaker than right; left ankle clonus and contracture left tendo Achillis. Spasticity of both legs.

Reflexes: Knee-jerks R. ++; L. +++; ankle-jerks R. +; L. ++; plantars, R. ↓; L. ↑↑. On sudden stimuli, triple flexion reflex, brisk in left leg, weak in right.

Sensation: Strong suggestion of delay rather than failure to appreciate pin-prick, cotton-wool, and hot and cold on right as compared with left leg; ? early Brown-Séquard syndrome. On upward stroking with cotton-wool or pin a more definite appreciation, posteriorly at level 1–2 L.V., anteriorly midway between umbilicus and symphysis.

Sphincters disturbed.

Cerebrospinal fluid: Clear, no clot, sterile. Cells, 10 lymphocytes: Protein 15 mgm.%; Pandy reaction negative; chlorides 740 mgm.%; glucose normal. Wassermann reaction negative.

Skiagrams show no vertebral abnormality. Lipiodol is partially held up at level L.V.1.

Provisional diagnosis: Intramedullary tumour at level 12 D—1 L.

Operation by Mr. Charles Donald (at Hospital for Sick Children, Great Ormond Street).—Arachnoiditis, with whitish appearance and some adhesions, particularly at level of L.V.1.

Present state.—Walking better than before operation but legs spastic, tendon-jerks exaggerated, and plantars extensor. Nocturnal enuresis. Slight sensory impairment up to level of umbilicus.

One point about this case is the age of the child. This condition is uncommon at 9. In a group of cases collected by Dr. StClair Elkington, the average mean age was round about the forties. The symptoms were first noticed in 1934, and the child

was in the National Hospital in 1935, but at that time the lipiodol rapidly descended without any " guttering ". The result of the operation is perhaps a little disappointing. This may be explained by the long history and the ischæmic changes which have occurred in the cord itself.

Toxic Hydrocephalus in a Girl at the Age of 10 Years.—W. G. WYLLIE, M.D.

Marjorie N., now aged 13 years.

At 10 years for a period of three months she had " bilious attacks " with frontal and occipital headaches, vomiting often before breakfast. There was some dizziness. During this period swelling of the optic discs up to 4 D developed in both eyes with three minute hæmorrhages in the right fundus. There was some nystagmoid jerks of both eyes on lateral deviation, and the pupils were dilated and reacted poorly to light. Otherwise the central nervous system was normal. The cerebrospinal fluid on three occasions was under considerable pressure, but was clear, sterile, and contained no increase of cells.

Past history.—Measles, chicken-pox, pertussis and scarlet fever, and tonsillectomy, all at a considerable period before above illness. No sore throat or earache at time of illness.

Mantoux reaction negative ; W.B.C. 6,700.

Progress.—In five months the swelling of both discs had disappeared, visual acuity $\frac{6}{6}$. The right disc edge shows a slightly ragged outline.

Scalenus Anticus Syndrome in a Girl Aged 11 Years.—W. G. WYLLIE, M.D.

For two months the patient has had intermittent aching pains in both arms, worse in the right arm from shoulder to wrist. Sensation of pins-and-needles in right arm, usually ulnar border, and in 4th and 5th fingers. Symptoms aggravated by carrying heavy objects, and in lifting the arms as in drill at school. Sensation of a weight pressing on the right shoulder. There is no definite muscular weakness.

Patient shows abnormal descent of the shoulders, or markedly sloping shoulders with an apparently long neck. X-rays show low position of shoulders and of first costo-chondral junction in comparison with normal anatomical type, and also large transverse processes of 7th cervical vertebra.

The symptoms are attributed to neuro-circulatory compression behind insertion of scalenus anticus into medial end of 1st rib.

It has been stated with regard to the drooping of the shoulder, that if the X-rays be focused over the level of the 1st dorsal vertebra, in cases of this kind the 1st rib will be seen to join the sternum at about the level of the 4th or 5th vertebral body. That is so here, and emphasizes the effect of the long scalenus anticus muscle. The irritation of the muscle itself is caused by its nerve of innervation which comes from the 7th cervical segment ; the 7th and 8th roots are the first to be irritated by the long muscle. Thus a vicious circle is set up—spasm of the muscle and increased irritation of the nerve. This child also has two rather emphasized transverse processes, and if the case had been older it might well have been regarded as a case of cervical rib of the old-fashioned diagnosis.

Dr. PARKES WEBER asked whether these large 7th cervical transverse processes had not formerly been regarded as a type of small 7th cervical ribs. He seemed to remember that about 1910, when cases with symptoms thought to be due to 7th cervical ribs were frequently shown in London, there were among them cases in which there were simply large transverse processes which were supposed to represent small 7th cervical ribs. Recently he had been shown a patient with the scalenus anticus syndrome in whose case he had previously suggested that there might be small 7th cervical ribs.

Left Trigeminal Pain, treated by Sjöqvist's Medullary Trigeminal Tractotomy (HARVEY JACKSON, F.R.C.S.).—REDVERS IRONSIDE, F.R.C.P.

Mrs. Emily W., aged 28 years. Factory hand.

Five and a half years ago, the patient complained of a boring pain over the left supra-orbital region and the left side of the nose. Submucous resection and tonsillectomy gave no relief. Three years ago a Caldwell-Luc operation was performed for antral polypi, on the left side. There was post-operative hæmorrhage, and the left jugular vein was tied. No relief of the neuralgia followed, and the left antrum continued to suppurate until nine months ago, when it was again operated on. This was followed by a facial abscess.

After this the patient began to have attacks of explosive pain in the distribution of the maxillary and ophthalmic divisions of the left trigeminal nerve. She was afraid to wash her face or touch it, and afraid to talk. Patient lost over 2 st. in weight, and was unable to eat in comfort. No sensory impairment on the face. Corneal reflexes brisk and equal.

Two months ago, Mr. Harvey Jackson performed Sjöqvist's medullary trigeminal tractotomy. Craniotomy. Unilateral cerebellar approach. Medulla exposed. A

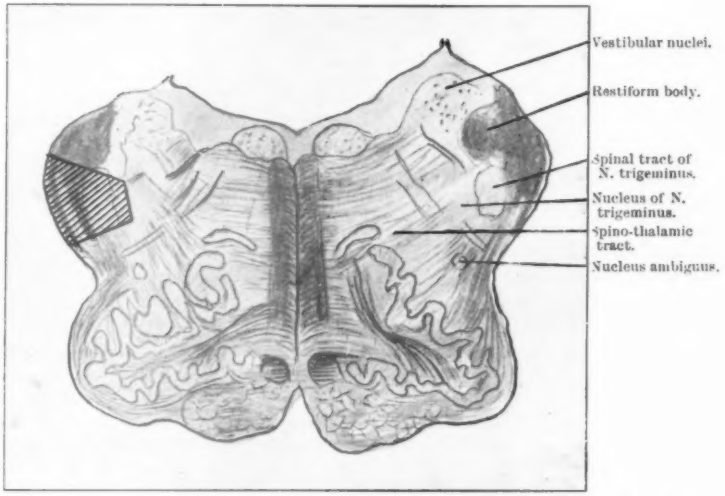

FIG. 1.—Transverse section of the medulla at the level of the middle of the inferior olive. Incision marked with lines (After Sjöqvist)

point was selected immediately caudal to the lowest vagus filaments and a few millimeters dorsally to them. The level of the incision corresponded to the border between the middle and inferior two-thirds of the eminentia olivaris. A guarded knife was inserted here for a distance of 3 mm. (fig. 1).

Uneventful recovery. No laryngeal palsy; no vertigo or ataxia; no sensory loss in trunk or limbs; pupils normal. Patient is now entirely free of pain. Left corneal reflex diminished. Dissociated anæsthesia on the face. Light touches of cotton-wool are everywhere appreciated normally. To pin-prick there is complete analgesia over the left forehead, cheek, and chin, including hard palate and gums of the left upper and lower jaw. The analgesia extends slightly across the mid-line. The tongue is spared. There is loss of appreciation of heat and cold stimuli over the

analgesic area. Deep pressure pain is appreciated on the left side of the face, as is vibration over the bony points. Masseters and pterygoids contract normally on the two sides, and lateral movements of the jaw are normal. Taste and smell unaffected.

This operation is probably not nearly as simple as it looks on paper. With regard to possible dangers, the commonest complication is paralysis of the recurrent laryngeal nerve. Again, if the incision is wrongly made, the patient may develop untoward symptoms, or the neuralgia may be unrelieved. The chief difficulty of the operation seems to lie in making the section high enough up to divide the fibres of the third division, and in this case the fibres from the tongue seem to have escaped altogether, suggesting that they are placed most cephalad in the bulbospinal tract (fig. 2).

The chief advantage of the operation is that the sensation of touch on the face is preserved.

One interest of the post-operative picture is in the various physiological points which arise, an outstanding one being the fact that the corneal reflex and the

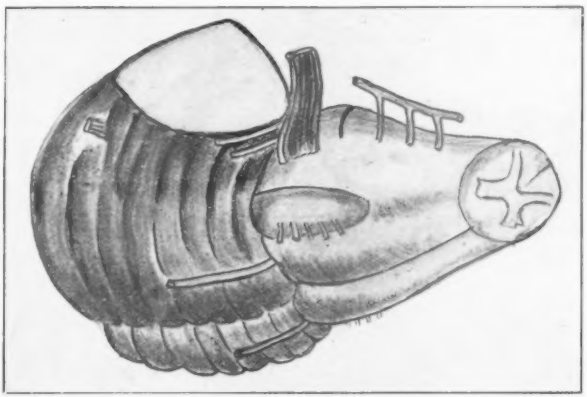

FIG. 2.—Position of incision in the medulla (after Sjöqvist), *Acta Psych. et Neurol.*, Suppl. 17, Helsingfors, 1938.

conjunctival reflex seem to disappear along with pain and temperature. Another point is that some cases which have had this operation show that temperature is most affected and sense of pain less so, while other cases will show that the predominant effect is a loss of pain sensibility.

Discussion.—Mr. HARVEY JACKSON said that the reason for trying out this operation in the first place was that he was presented with a patient who had Paget's disease and first and second division trigeminal neuralgia. It was the case of a young man, and he thought it an ideal one for this type of operation, suffering as he did from first and second division pain. The difficulties of the operation were not really great to one who was used to exposing that part, but one had to be particularly careful about the hæmorrhage from the pia mater, which must be separated from medulla before the section was made. The anterior extent of the incision was very roughly about 1 mm. behind the vagal root, the depth 3·5 mm., and total length 4·0 mm.

Dr. WILFRED HARRIS said that the chief advantage of Sjöqvist's operation was the preservation of tactile sensation on the tongue and jaws, so that eating on that side was not subsequently interfered with. It is therefore more specially indicated in cases of neuralgia of the jaws than in this case, in which the neuralgia implicated especially the ophthalmic division. Here an alcohol injection of the inner portion of the ganglion would cure the neuralgia permanently, with less risk.

Parasagittal Meningioma of Pre-natal Origin.—WYLIE MCKISSOCK, F.R.C.S.

J. D., a girl aged 10 years, was admitted to this hospital in February 1937, with a history of weakness of the left ankle since birth and dragging of the left foot since she began to walk, at the age of 1 year. She was otherwise a normal child until six months ago, when she began to have sensory fits involving the left hand and arm, followed by transitory weakness. Three days before admission she had right temporal headache for the first time and vomited on several occasions.

Neurological examination.—The positive findings were bilateral papillœdema of long-standing appearance, inco-ordination of the left hand and left leg, spasticity of the left leg and weakness of the left leg, most marked at the ankle. The left abdominal reflexes were diminished, the left knee- and ankle-jerks were increased, and there was a left extensor plantar response.

X-rays showed a conical spur of bone to the right of the mid-line in the parietal region and evidence of prolonged high intracranial pressure.

Ventriculography was attempted but neither ventricle could be found. Electro-encephalography showed evidence of generalized high intracranial pressure and rendered accurate localization impossible.

Operation (1.3.37).—A large right-sided osteoplastic flap was turned down to expose a very large tumour, the upper surface of which was attached to the spur of bone seen in the radiogram. The growth was also attached to the superior longitudinal sinus for 2½ in. and to the falx down to the inferior longitudinal sinus from which it was also growing. Neither sinus appeared to be occluded, and the tumour was accordingly cut through about half a centimetre from this broad attachment and removed, together with the area of bony attachment above.

Post-operative course.—This was uneventful until the fifteenth day when sudden weakness and flaccidity of the left hand and arm occurred. This slowly disappeared and the patient was discharged eight weeks after operation, with slight weakness only of the left arm and leg, intention tremor of the left hand, and the left foot-drop which had been present from the first few months of life. The papillœdema had entirely subsided but the left plantar response was still extensor.

Subsequent course.—Three months ago the patient awakened one morning with profound numbness and weakness of the left hand and arm. Examination revealed a great degree of cortical sensory loss, with considerable diminution of power in the affected extremity. Otherwise there was no change in her physical condition.

Since this sudden catastrophe the condition of the left arm has slowly improved, and the local condition is now much better although far from normal. The area of decompression has been flat and sunken ever since discharge after operation.

The only possibility of cure in this case would appear to be to resect the falx over the affected area together with about 2½ in. of both sinuses, and I should like the opinion of this meeting as to when this somewhat hazardous procedure should be undertaken.

This case has perhaps only two points of interest. The first is that the disability was noticed in the left foot certainly before the child started to walk. It seems to suggest that the tumour, which was very large when operated on, probably was present before the child was born. The other point which is of interest to me is due to the findings at operation. There was attachment to the whole falx right down to the inferior longitudinal sinus, to which there was also attachment for at least 2 in. What I particularly want to know is when removal of the remainder of the tumour should be attempted. It involves removing very nearly 3 in. of the falx. How long can one leave the child before attempting this, and how much damage is one going to do by the removal ?

Discussion.—Dr. ANTHONY FEILING said that he was interested in this case because the patient had been under his own care. He wondered whether members would agree that the recent paralysis of the left arm was probably due to thrombosis of cortical veins, most likely arising from damage to the superior longitudinal sinus.

The PRESIDENT said that if thrombosis of the cortical veins due to damage to the superior longitudinal sinus had already occurred the answer to Mr. McKissock's question was that he could now operate at any time.

Mr. G. C. KNIGHT said that two years ago, being forced in one case to leave a thin layer of tumour tissue on the side of falx he had coagulated this very thoroughly. Six months later he opened up again and was unable to see any trace of the tumour at that time, and the patient had remained well since. It might be worth while in Mr. McKissock's case to coagulate the parts very thoroughly as a preliminary step.

The PRESIDENT said that what Mr. Knight had suggested would depend upon whether the homolateral veins were going to prove efficient.

Alzheimer's Disease.—R. G. M. LONGRIDGE, M.R.C.P. (for Dr. DOUGLAS MCALPINE).

E. L., a married woman aged 56 years, suffering from progressive loss of memory and speech defect noticed for about five years.

Family history and past personal history.—No relevant facts.

Present history.—Inability to articulate the words she wants to use. Unable to do shopping owing to defective memory. Cooked the Sunday dinner up to date of admission (August 27, 1938), and tells her husband to make the beds or to do odd jobs which she is unable to do herself.

On examination.—Cranial nerves: Optic discs normal. Moderate retinal arteriosclerosis. Partial homonomous right hemianopia. Optokinetic nystagmus absent to the left, diminished to the right. Pupils normal. External ocular movements normal. Hearing normal. Apraxic inability to protrude the tongue.

Motor system: Difficulty in relaxing the limbs but tone appears normal. Slight wandering of right arm when outstretched. Power good in all muscle groups. Coördination normal. Reflexes: Brisk in all tendons and increased on the left. Grasp reflex absent. Abdominals not obtained. Plantar responses flexor, but less definitely on the left.

Sensation: Joint sense normal in both hands. Doubtful impairment of postural sense in fingers of both hands, which may be due to agnostic loss of body concept. No gross loss of touch localization, and stereognosis normal. Compass-point discrimination normal.

Cardiovascular system: Accentuated aortic 2nd sound with ringing quality. Blood-pressure 145/85.

Nothing abnormal found in lungs or abdomen.

General behaviour: Apathetic and content, but upset at failures at examination. Unable to give an account of her illness. Memory for distant events extremely incomplete. She is disorientated in time and imperfectly orientated as to place, but orientated as to her identity. She has fair insight.

Sensorium: The patient understands spoken language, but shows impairment of understanding of print and of pictures, and is quite unable to read handwriting. Music recognized as a special auditory stimulus, but rhythm not appreciated Single figures are recognized but numbers of more than one figure are not understood. No definite astereognosis allowing for aphasia.

Finger agnosia was almost complete. Some agnosia of body concept and of left side was shown. Right and left cannot be identified.

Visual orientation was normal in both fields.

Memory: Visual and auditory memory are almost completely lost. The patient was unable to remember her name, whether she had brothers and sisters, or what colour was the bus which her husband used to conduct. Objects were pointed out to her in a room but she could only enumerate two out of six, and could not give any idea of the relative size of the room or the number and position of windows immediately on return to her ward on the same floor. Visual imagery is almost completely lost; she cannot describe or visualize a dog or a cat. Retention is practically abolished; the name of the hospital was forgotten in two minutes and she cannot repeat four figures, but she can frequently remember what she had for a meal earlier the same day or the previous day.

Speech: Vocabulary small, and conversation extremely limited. Sometimes she cannot name objects, sometimes she names them wrongly without knowing it, and sometimes she cannot articulate words.

Agraphia: Unable to write anything, even her name.

Acalculia: 3 + 3 = "4"; 1/- − 6d. = "6d." (oral); 12 − 6 = "6" (oral). On another occasion 3 × 3 = "9" (oral); 2 × 3 = "2" (oral); 3 tuppences = "2" (oral). Asked to add 2 and 2 on paper, she just scribbled over the figures.

Apraxia: Automatic actions are normally executed as shown in feeling objects in her hands, using scissors, sewing, &c. Ideational acts are performed badly with both hands, worse on the left, and produce perseveration.

Constructional apraxia: The patient is unable to draw a square or circle or a simple representation of a house, even with an example to copy. She traced a very irregular line with many kinks and loops on attempting each of these. Attempting to cut a circle out of a sheet of paper to a copy, she tried first to pierce the paper with the scissors and when she was started on cu ting, made a spiral cut ending with practically nothing (Mayer-Gross's closing-in sign).

Lumbar puncture: Pressure and fluid normal. Blood Wassermann reaction negative.

Electro-encephalography showed a well-marked δ-focus in the middle fronto-temporal region on the left.

Encephalography showed gross internal hydrocephalus more marked on the left than the right, and very little air over the cortex.

Progress: After the encephalogram the patient had a period of confusion, with motor activity at night, lasting ten days. She would get up and cover patients with newspapers without realizing what she was doing. Double incontinence occurred during this time only.

Discussion.—Dr. DOUGLAS MCALPINE said that in diagnosing this case he had felt that the process was much more widespread and extended more posteriorly than did most cases of Pick's disease, and for that reason it was put down as an example of Alzheimer's disease. The loss of visual imagery was marked. The woman was quite unable to describe an animal such as a dog.

Dr. MACDONALD CRITCHLEY said Alzheimer's disease was one arrived at largely by a process of elimination. He thought Pick's disease unlikely here, partly because of the hemianopia which suggested interference with long projectional tracts. Moreover, the failure to demonstrate by encephalography any regions of cortical atrophy was an important point.

Dr. N. S. ALCOCK asked whether Dr. Longridge and Dr. McAlpine were satisfied that there was not a thalamic tumour, which possibly might cause the internal hydrocephalus.

Mr. DOUGLAS NORTHFIELD supported that suggestion. He noticed in the ventriculograms a slight enlargement of the basal ganglia on one side, and that the 3rd ventricle was very inadequately filled with air.

Dr. LONGRIDGE considered that other features of the case ruled out any obstructive cause.

Mr. NORTHFIELD said that the obstruction might not be complete.

Dr. DOUGLAS MCALPINE said that he could not visualize how a thalamic tumour was going to produce these various forms of agnosia and apraxia while at the same time the postural sense and other forms of sensation were conserved.

Infantile Hemiplegia. Cerebral Angioma. Subarachnoid Hæmorrhage.—G. C. KNIGHT, F.R.C.S.

J. H., aged 13 years, admitted to West End Hospital, October 24, 1938.

Patient was well till seven weeks ago. Vomited several times in one day. Next day was "out of sorts" and following day pain in neck developed which spread over head and down back to loins. Neck rigid.

Lumbar puncture at Princess Elizabeth of York Hospital: 30 c.c. of blood-stained fluid was removed under increased pressure, with immediate relief of the headache. Microscopically the fluid was full of crenated red cells. The fluid was definitely xanthochromic.

19.8.38: Head still retracted with great nuchal rigidity. Further lumbar puncture was done with the same result as on admission. Thereafter the child's condition gradually improved. The headache and rigidity disappeared, and on 15.9.38 lumbar puncture was entirely negative.

Past history.—Right arm and leg weak since childhood; first noticed by parents at the age of 2.

On examination.—Visual fields and fundi normal. All right-sided reflexes slightly increased. Right extensor plantar response. Tone of the right side greater than left. Power diminished, especially dorsiflexion of foot. Sensation was normal.

Cerebrospinal fluid (25.10.38): Clear and colourless. No tint of blood. Cells, 2 per c.mm. Small lymphocytes only. No R.B.C. Total protein 0·015%.

Globulin: No excess.

Wassermann and M.K. reactions negative.

Lange's test 0011000000.

Skiagram of skull (25.10.38): Small area of calcification in left frontal region, ? choroid.

Arteriography (27.10.38): 20 c.c. thorotrast injected under local anæsthesia. All vessels except the middle cerebral are well filled. The left middle cerebral is replaced by a diffuse opacity and a number of small converging vessels.

(Patient did not attend the Meeting.)

Section of Ophthalmology

President—Malcolm Hepburn, F.R.C.S.

[*October* 14, 1938]

The Nomenclature of Diseases of the Fundus

PRESIDENT'S ADDRESS

By Malcolm Hepburn, F.R.C.S.

For many years I have been impressed by the multiplicity of names given to the various diseases of the fundus, and the unsatisfactory nature of some of them. We sometimes find the same name applied to two totally different fundus pictures, and different names given to the same picture, so that instead of clarifying our ideas and producing in our minds a definite mental picture of any particular type, it appears to lead to further confusion, and merely ends in creating an ever-increasing number of entities, many of which are entirely unnecessary. Moreover it fails to provide the basis for any reasonable classification and renders difficult an accurate diagnosis on which any successful line of treatment must ultimately depend. For example, in the "American Encyclopædia of Ophthalmology" there are no less than twenty-six different forms of choroiditis alone, classified indiscriminately according to the pictorial figure, position, or clinical causes.

It seems to me, therefore, that a re-examination of fundus conditions in the light of recent pathological work is long overdue and it is particularly desirable that some sort of agreement should be arrived at, if possible internationally, regarding the nomenclature of diseases of the fundus from a descriptive and literary point of view, as well as from a clinical standpoint. Many conditions for which new names are invented are merely stages in the same pathological processes which may develop gradually and produce some alteration in the fundus pictures from time to time, the name given to many of these cases often depending on the stage in this development at which the fundus is first seen, and it is by concentrating too much on these variations and other small details that the actual cause of them has been lost sight of, and thus new names are continually being created.

Every disease of the fundus is a definite pathological or congenital condition which should receive its appropriate name comprising all possible details. Considering the amount of pathological work done by ophthalmologists in different countries during recent years, it seems to me that we are belittling their work if we continue to describe so many fundus diseases entirely in terms of a picture, or according to their shape, or the position they occupy. Moreover, the responsibility entailed in giving a title to a paper or in compiling a textbook with illustrations, which is to take its place in ophthalmic literature, is not sufficiently realized. We, as an ophthalmic profession, by our descriptions, are establishing a nomenclature which is supposed to be regarded as authentic and is permanently recorded; it is also accepted without question by those who do not belong to our special branch. We are at the same time handing down to future generations names which ought to be available and useful for purposes of research; but if the names fail to give any clear indication of what we expect to find, the difficulties of our investigations are immensely increased. I have personally experienced this difficulty on many occasions, and especially in preparing this address, and have come across so many ambiguous names and titles that I have only time to select a few examples, and to illustrate from them the lines on which any new nomenclature might be based.

Now, when a case is described as one of embolism of the central artery of the

retina, or optic atrophy, or thrombosis of the central vein, we all have a clear mental picture of what we expect to see when looking at such a fundus. We do not speak of the cases, respectively, as œdema of the macula, or white disc, or hæmorrhagic retinitis, and yet these pictorial details are present in each case.

I claim that many diseases which now carry ambiguous names could be described in similarly intelligible language. I do not wish to imply that all abnormal conditions of the fundus are going to be easy to interpret by any method on which we decide; there will always be a certain number of diseases which will baffle the most experienced of us and will be difficult to put into words. But at the present time there are many names which are used in different senses by various observers; some are actually meaningless, while others are quite wrong and should be expunged from our ophthalmic vocabulary altogether. It is from this angle that I am approaching the subject in this paper because, until we reach agreement on these points we cannot even commence

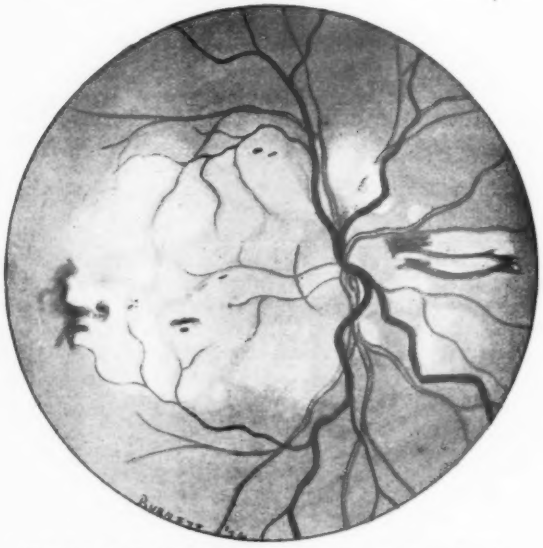

FIG. 1.—R. Fundus, July 1, 1924. Traumatic asphyxia.

to construct the fundamental principles of a new nomenclature. I shall not mention any writer by name or indicate the sources from which I have obtained my information, because, although I am bound to adopt a critical attitude, I do not wish to introduce any personal controversy into a presidential address; I will only say that I have selected drawings and titles from published works of ophthalmologists of several nationalities. If, however, any author happens to recognize his own production, I am afraid I cannot very well help it.

In the first place, it is just as well in choosing the title of a paper to give some indication that the name refers at any rate to some part of the eye. For instance, I found a paper entitled "A case of traumatic asphyxia", a condition which occurred as the result of a motor accident. I imagined, therefore, that I should see the picture of a man with broken ribs suffering from distressing dyspnœa, and an attendant standing by administering relief from an oxygen cylinder. Instead of which I find the following (fig. 1): This is evidently a severe choroidal hæmorrhage at the macula.

Then why not have described it as that? We should then have had some idea of what to expect.

I will deal with the subject under five headings: (1) Names used in the wrong sense. (2) Pictorial descriptions. (3) Topographical descriptions alone. (4) Topographical descriptions without qualification. (5) Different names applied to the same picture.

Names Used in the Wrong Sense

There appeared in a recent textbook by a well-known ophthalmic surgeon, the following drawing with the title "gyrate atrophy" (fig. 2). I may add that the surgeon was not personally responsible for this wording, but it will pass out into ophthalmic literature as authentic. Now, gyrate atrophy of the choroid and retina

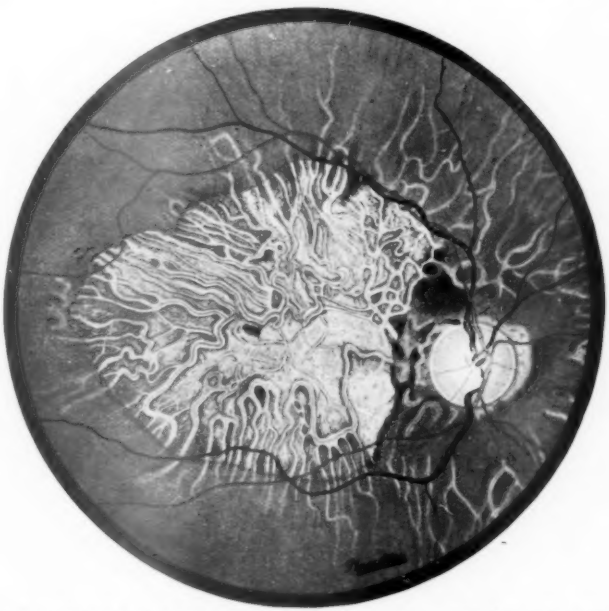

Fig. 2.—Sclerosis of choroidal vessels at the macula. Called gyrate atrophy.

was the name given to an extremely rare congenital condition, possibly allied to choroidoræmia, found in three young females of one family and described by Fuchs in 1896; a black-and-white drawing was published by Cutler about the same time. There was no coloured picture, but I have had one reconstructed according to the illustration and description in the paper, and this I now show (fig. 3). There must be something wrong here.

The first drawing, which is not very uncommon, shows a patch of sclerosis of the choroidal vessels at the macula, with probably secondary degeneration of the retina over it, but those who do not happen to know what gyrate atrophy looks like will be prepared to accept the first picture without question merely because of its authorship. This is one of the ways in which wrong names are perpetuated.

From the clinical side, which should always be considered before we come to a decision on any fundus disease, the difference between these two pictures is equally

striking. In gyrate atrophy the subjects are young people, who suffer from night-blindness in addition to defective central vision, whereas in sclerosis of the choroidal vessels at the macula the subjects are elderly people whose central vision is also well below normal, but they see better in a dull light.

Another term which is very loosely used is choroiditis. The only time when this description is realiy applicable is during the acute stage of active inflammation of the choroid, in the same sense as we use the word iritis. When we use the term iritis in describing a case we expect to see the iris in a state of acute inflammation with the usual signs associated with such a condition ; and not a quiet eye with some iritic adhesions and spots of pigment on the anterior capsule.

FIG. 3.—Gyrate atrophy.

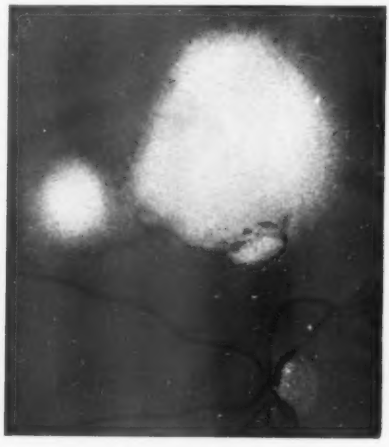

FIG. 4 —Acute choroiditis.

Here is a picture of what is well known to be choroiditis (fig. 4) ; but this (fig. 5) is also described as retino-choroiditis, and I have known these cases treated as one would treat an acute case. The condition in the next case also (fig. 6) is often called retinochoroiditis, but I know that there has never been choroiditis in the case because I have watched it from its earliest stages. The condition began as an ill-defined wedge-shaped area of œdema extending downwards and inwards from the disc and entirely independent of the retinal vessels which passed over it unaffected. When the œdema had subsided the area entered the scarred stage, with the migration of pigment common to all choroidal affections, thus establishing the diagnosis of obstruction of one of the choroidal vessels. The distribution of the pigment is entirely different from that seen in inflammatory cases, the cause is different, and the treatment to be adopted, even though it fails to restore vision in the affected area, is different also. The final stage of choroidal inflammations is that of white fibrous tissue-scarring, with pigment proliferation in varying quantity in the immediate vicinity. This leads me to speak of the term atrophy, which is so often applied to white areas seen in the fundus, especially those following inflammations. I suppose it is possible for true atrophy of the choroidal stroma to occur, producing gaps in its structure and revealing the sclera beneath—just as we sometimes see atrophy of the iris stroma following repeated attacks of iritis and iridocyclitis—but in the majority of cases the white areas resulting from inflammations of the choroid have been proved by pathological

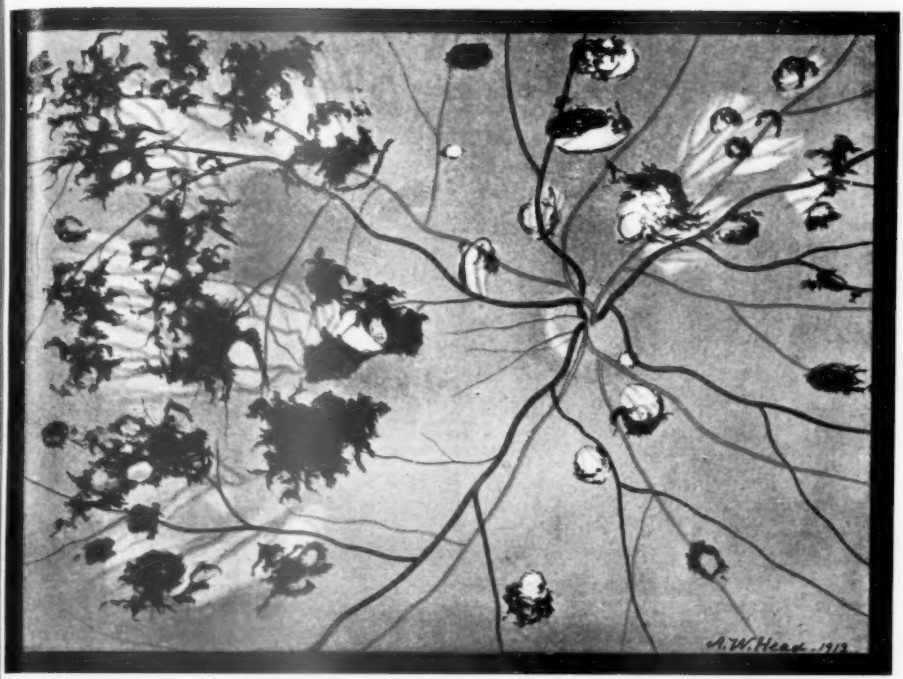

FIG. 5.—Multiple choroidal scars.

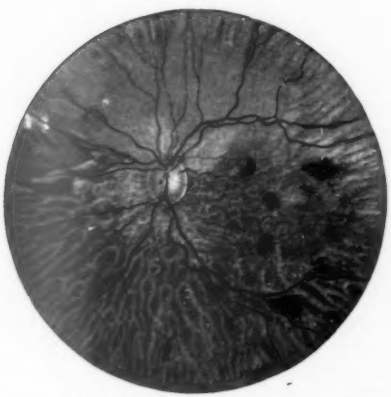

FIG. 6.—Sclerosis of some of the choroidal vessels, showing scarring and pigmentation.

examination to be due to fibrous-tissue formation and the cases are not cases of atrophy at all. Yet we still hear and read of atrophic patches seen in the fundus, perhaps more often in cases of myopia where the white areas are due to exposure of the

sclera through gaps in the choroid caused by stretching. The term atrophy is therefore very seldom used in its right sense and should be avoided.

I have heard of certain cases of inflammation of the choroid designated as progressive and put into a special category by themselves. I do not quite understand the meaning of the word " progressive " as applied to inflammatory affections, nor

FIG. 7.—Choroidal scarring—so-called progressive type.

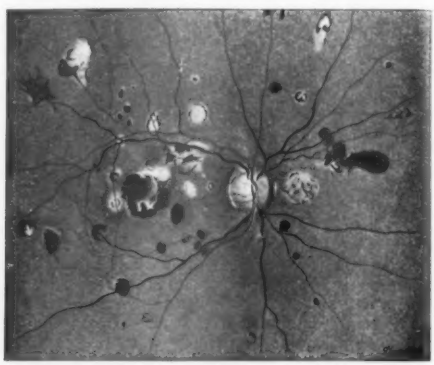

FIG. 8.—Choroidal scarring of progressive type in early stage.

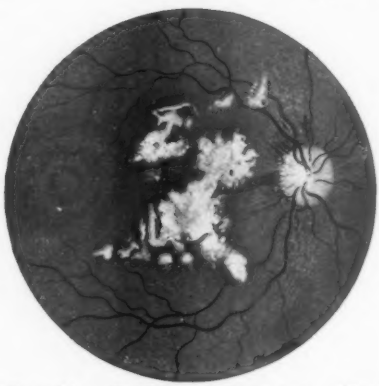

FIG. 9.—Retinitis. True inflammatory type. Nephritic.

do I remember having seen any communication or paper bearing this title, but I am informed that the following case (fig. 7) is one belonging to this type, and that this next one (fig. 8) is the same condition in an early stage, which has now, after a period of eleven years, become like the first one. I have my doubts about the appropriateness of this title as applied to inflammations.

Retinitis.—Strictly speaking, this term should only be used in fundus conditions in which the exudations are the result of inflammation of the retina (fig. 9), but it has been used to describe any form of albuminous exudate which happens to be situated in the retinal tissue, many of which do not originate in the retina at all but are forced into the retinal layers from the choroid, because of the magnitude and quantity of

the original extravasation. Considering the extremely rich blood supply of the choroid, as compared with that of the retina, it ought not to surprise us that many cases of massive exudate, especially at the macula, are very likely to be due to some disease of the choroidal vessels. There is plenty of evidence from pathological records in many countries to support the view that large exudates may come either from the retina or the choroid, and therefore the word retinitis should not be used in this connexion.

The special cases of massive exudate described by Coats and examined by him pathologically, were proved to be retinal in origin. Here is Coats' original picture (fig. 10), which is typical of all the five cases he examined. The three leading features in all his cases are : (1) The presence of extensive white masses of exudate covering large areas of the fundus, very widespread with no definite limitations and associated with some abnormality of the retinal vessels ; (2) the tendency for this exudate to avoid the macula, and (3) the fact that the subjects are all young people. Therefore the nearer the macula a massive exudate appears, the more circumscribed it is, and the older the patient, the less likely is the case to be one of Coats' disease. Yet I have

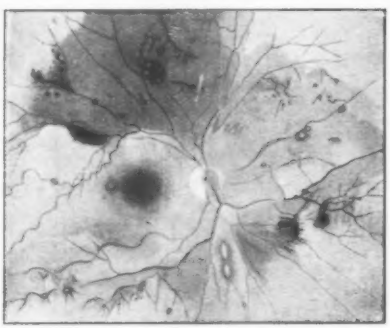

FIG. 10.—Coats' case of massive exudate.

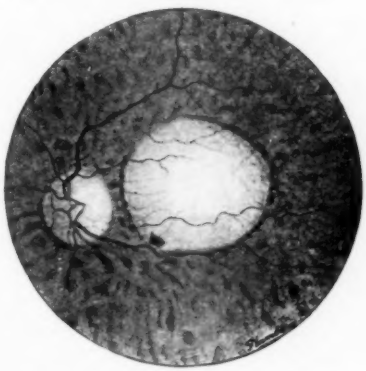

Fig. 11.—To illustrate what is not Coats' disease. Called senile macular exudative retinitis.

heard this name applied to all sorts of exudates, even those near the macula, and with well-defined boundaries (similar to fig. 11).

Retinitis pigmentosa is another wrong name because, as everyone knows, the condition is not an inflammation of the retina, but a degeneration accompanied by migration of pigment. A better name for it is pigmentary degeneration of the retina, which is called primary when it is associated with little change in the underlying choroid and often beginning in young life, and secondary when the choroid shows varying amounts of fibrous tissue development such as accompanies sclerosis of the larger choroidal vessels. At the same time we all have a clear mental picture of what we mean when we talk of retinitis pigmentosa and it is shown in fig. 12. The slightest departure from this well-known picture I have seen described as " atypical ", but I cannot understand why a new name should be invented because of slight variations in the amount of pigment seen in the picture. Here are some drawings to illustrate this. Fig. 13 shows rather more pigment and the next more fibrous tissue development than usual, and on this account the migration of pigment is mechanically prevented from taking place in great quantity (fig. 14) ; and here is another case (fig. 15) where there is a good deal less than the normal amount of both choroidal and

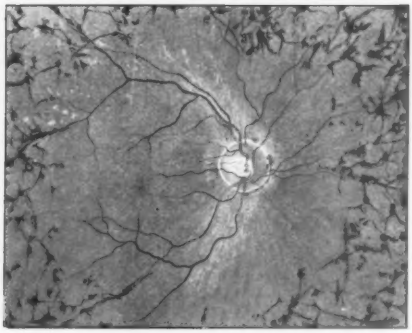

FIG. 12.—So-called retinitis pigmentosa.

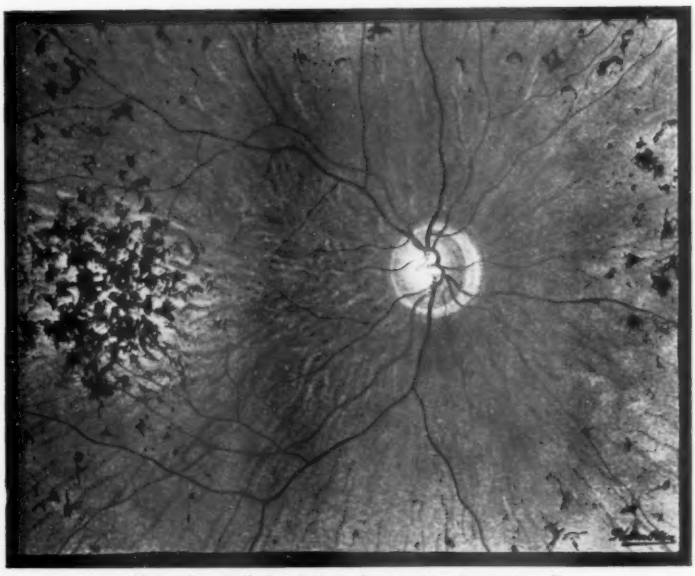

FIG. 13.—Called "Atypical retinitis pigmentosa."

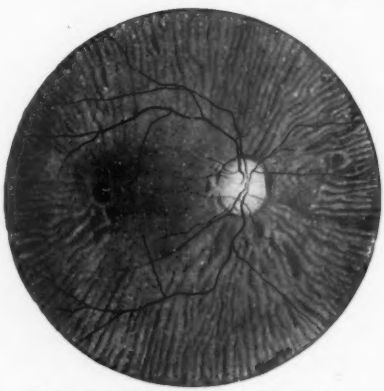

FIG. 14.—Called "Atypical retinitis pigmentosa."

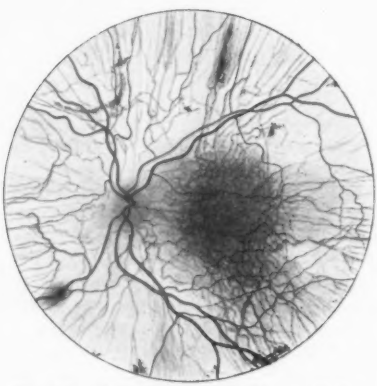

FIG. 15.—Another example of so-called atypical retinitis pigmentosa.

retinal pigment, and therefore less to migrate ; but in both cases what there is of the pigment is present in the usual situation. I do not know what the field of vision is in the case from which fig. 14 is taken, but fig. 15 shows the ordinary characteristics of the field of a primary pigmentary degeneration of the retina. There is not sufficient alteration in the picture to justify the establishment of a new entity.

Again, because various forms of degeneration occur in long-standing exudates in the retinal layers, and amongst them hyaline degeneration, this particular histological change is sometimes given undue prominence, and all forms of fundus conditions whice show retinal exudates containing such degeneration are collected together in the samh group and described under the heading " hyaline dystrophy ". On looking into a paper bearing this title, one cannot help being struck by the fact that many conditions are included and discussed which have nothing whatever to do with each other. I cannot think that it is the right principle to single out one particular histological change from the rest and build upon it a name which has an air of diagnostic finality but which is incomplete and of no practical value.

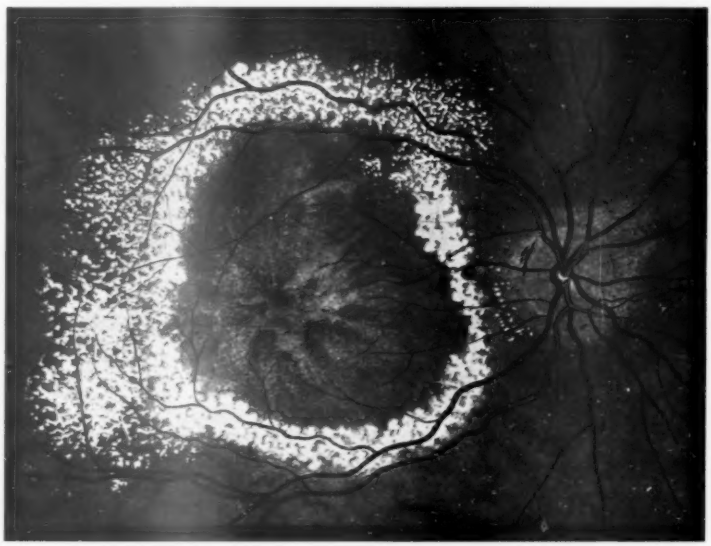

FIG. 16.—So-called retinitis circinata (complete ring).

PICTORIAL DESCRIPTIONS

I would put in a definite plea for the abandonment of pictorial names in diseases of the fundus as far as possible, or those bearing the names of the observer who first described them. Pictorial names are only justifiable when the pathology is not known, and those bearing the name of the original author are troublesome because it requires a double effort of memory to recall the particular condition to one's mind. Instances of pictorial descriptions are : Retinitis circinata, honeycomb choroiditis, striate choroiditis, guttate choroiditis, amongst others.

Retinitis circinata is merely a particular appearance of a rather massive exudate arranged round a central focus which is usually at the macula (though I have seen a similar picture in other parts of the fundus). Sometimes it forms a complete ring round the macula (fig. 16), and sometimes only a partial one (fig. 17) ; it all depends

on the amount of the original exudate which is again dependent on the severity of the lesion which has caused it, or on how much absorption has taken place before the case is seen (fig. 18). In a large proportion of such cases there is definite visible disease of the choroid at the macula, which may of course be inflammatory but is much more likely to be due to disease or obstruction of the choroidal vessels in this situation. Large deposits of exudate are also found in diseases of the retina alone (fig. 19); but they are not, as a rule, quite so massive, and although they may be inclined to encircle the macula, they are never so likely to form a complete ring and the central region shows no abnormality. This condition is not a special entity and the name should be given up.

Honeycomb choroiditis was first described by Doyne, and I am glad to be able to show you his original drawing through the kindness of Mr. P. T. H. Adams who has

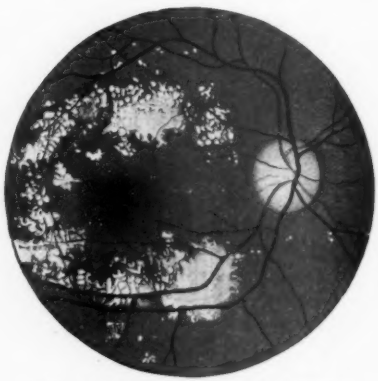

FIG. 17.—Another case, not complete ring.

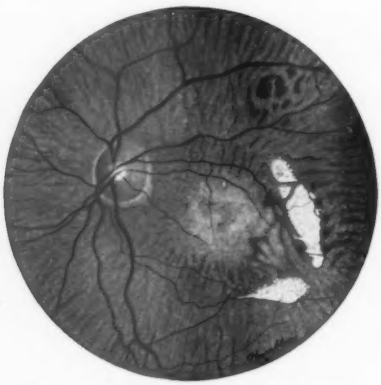

FIG. 18.—Another case, where some absorption has taken place.

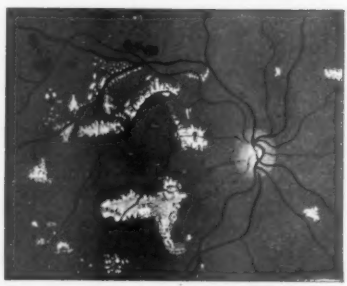

FIG. 19.—Retinitis circinata of retinal origin.

lent it to me (fig. 20). This is a very good pictorial description but it shows merely one of the variations in the appearance of a massive exudate which has formed round a central choroidal lesion at the macula, probably a vascular obstruction. But some exclusively retinal exudates due to renal or vascular causes, if excessive in amount, may assume a honeycomb appearance; and therefore since this condition may belong either to the retina or choroid alone, the name is ambiguous and should be avoided.

Striate choroiditis is the title of another paper, and in this case I expected to see some strange form of choroidal scarring, instead of which the picture suggests one of the varieties of angeoid streaks (fig. 21).

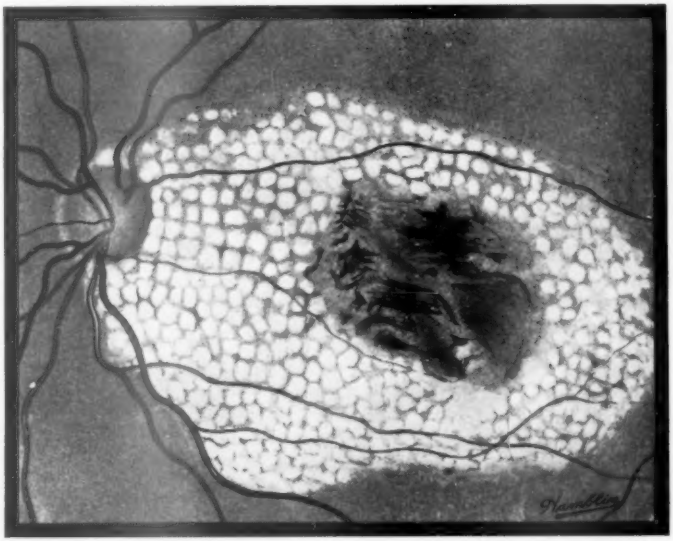

FIG. 20.—Honeycomb choroiditis.

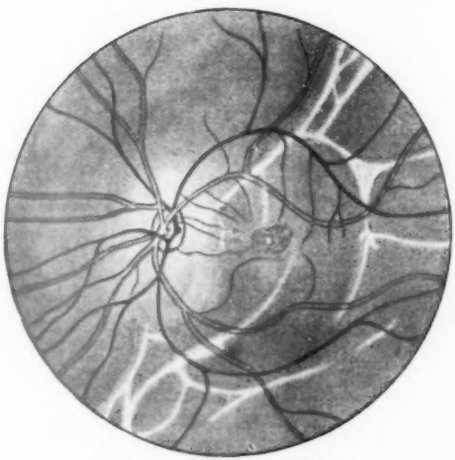

FIG. 21.—Striate choroiditis.

(M. Vianna, *Annales d'oculistique*, 1936, **173**, 956.)

The author makes a great point of stressing the importance of a few small differences between his case and other cases of angeoid streaks which I do not think are

sufficiently convincing to justify a new entity. It has by no means been definitely proved that all angeoid streaks are choroidal in origin, indeed some have been shown to be retinal. In any case striate choroiditis is a bad name, and until we are sure of a pathological explanation to account for them all it is better to retain the old one.

Guttate or Tay's choroiditis is another term which should no longer be permitted. It is now known definitely that this appearance has been proved pathologically to be due to hyaline or colloid degenerations of the membrane of Bruch which are not usually associated with any deterioration of vision, whereas any form of choroidal scarring would affect the sight (fig. 22).

Topographical Descriptions Alone

One example of these is the form of choroiditis known as *choroiditis juxta-papillaris*, first described by Jensen and called by his name. Some choroidal scars adjoining the disc are associated with sector-shaped defects in the visual fields, extending out into the extreme periphery (fig. 23). There is nothing special about this scar, but here is the field (fig. 24). Now this class of case, being characterized by a special name, would lead us to conclude that this type of scotoma is present only in scars near the

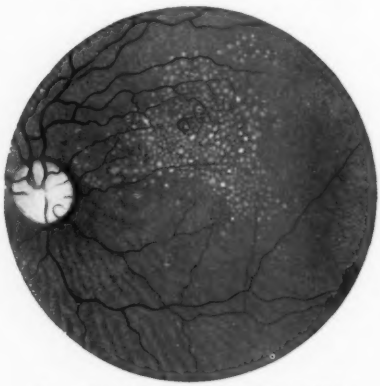

Fig. 22.—So-called Tay's choroiditis with pigment round edge.

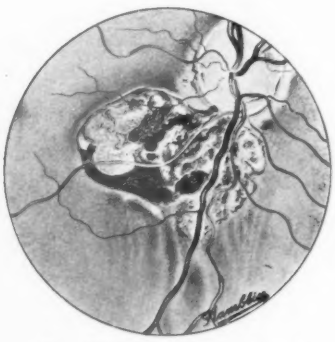

Fig. 23.—Choroidal scar near disc.

disc, but such is not the fact. Wedge-shaped scotomata are associated with scars, generally fairly large ones, situated in any part of the fundus, and I have several of such instances amongst my field charts. Therefore this position of a choroidal scar is no reason for its being classed as a new entity.

Another term under this heading is *macular disease*. This is a meaningless expression because the macula is only a region and not a structure, and one never knows what one is going to find in a paper bearing this title. If it conveys anything to one's mind it suggests that there is one particular affection which attacks the macula alone, and never any other part of the fundus, which, however, is not a fact.

I have every sympathy with the term " diseases of the macular region ", because there is no doubt that for some reason or other certain affections of the retina and choroid are prone to attack this part of the fundus more frequently than elsewhere (e.g. certain massive exudates, stretching and ruptures of the choroid, and some retinal degenerations) and this matter requires careful investigation and special classification ; but there is no disease peculiar to the macula alone—except, possibly, retinal degeneration, found in amaurotic family idiocy.

TOPOGRAPHICAL NAMES WITHOUT QUALIFICATION

Macular degeneration is one of these. I know of no name which is surrounded with so much ambiguity as the term degeneration, nor is the situation made any clearer by separating it into the two subdivisions of dystrophy and abiotrophy. From a careful study of these terms and the writings of those who advocate them, I have come to the conclusion that the only meaning one can attach to such expressions is that there is no particular reason why a certain proportion of diseases of the fundus should happen, and therefore there is no object in trying to discover the cause or thinking out any line of treatment by which they may be avoided.

Unfortunately, in the present state of our knowledge there are several diseases of the fundus which have to be placed in some such category as this, but the list of

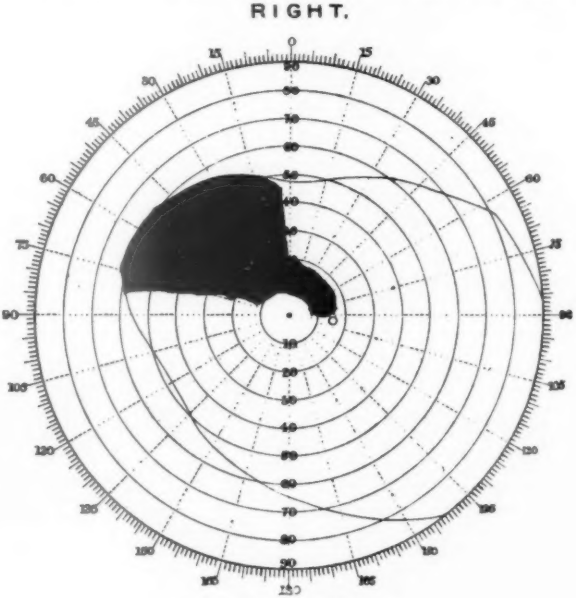

FIG. 24.—$\frac{1.0}{330}$ white.

dystrophies and abiotrophies is continually being added to by the inclusion of diseases which I really did think we knew something about, and others which certainly are not primarily degenerations and never have been.

Soon we shall be encouraged to settle down complacently—both scientifically and clinically—into a state of masterly inactivity, which is hardly compatible with true progress, nor in the interests of the patient who is chiefly concerned.

Macular degeneration is almost as meaningless as macular disease and for similar reasons.

Does this mean hyaline degenerations of the membrane of Bruch which is stationary and has generally no permanent effect on the vision, does it mean degeneration of the retina which may be progressive and ultimately lead to loss of central vision, or, again, does it mean hyaline degeneration which sometimes takes place in massive exudates upon which so much stress has lately been laid, or some other kind of degeneration ? It may be said, that of course this term refers to pigmentary degeneration of the retina at the macula, since other forms of degeneration of the retinal

layers do not show any visible changes and eventually lead to optic atrophy. Have we, however, actually reached final agreement on this point ?

I have found a paper entitled " disc-like degeneration of the macula ", and here is a case which might fairly be described as one of retinal degeneration in a disc formation (fig. 25), but on referring to the text of this particular paper I find a great deal of attention is paid to the fundus details in a series of seven cases. There were no illustrations, but the authors speak of large, greyish-yellow masses at the macula with so-called retinitis circinata surrounding them, similar to this picture (fig. 26)

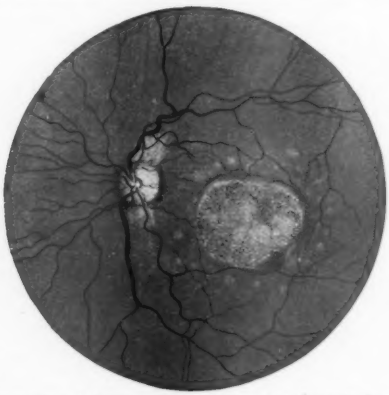

FIG. 25.—Degeneration (pigmentary) of retina at macula in disc formation.

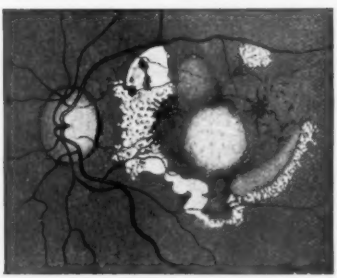

FIG. 26.—What has been described as disc-shaped degeneration.

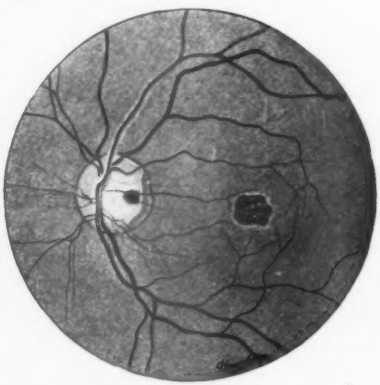

FIG. 27.—Hole in retina at macula.

and in one case a microscopic pathological examination was made and changes in the choroidal blood-vessels were discovered. The difference between the pictures illustrating such conditions and that of pigmentary retinal degeneration is so great that we cannot possibly tell what we shall find when looking up the literature bearing such an indefinite title. Obviously there is no unanimity regarding the picture designated by the term macular degeneration.

Another name under this heading is that of " macular holes "—which has no special meaning by itself. In what structure is the hole ? I know what a hole in the retina at the macula looks like, and fig. 27 is a drawing of one; but another

class of case has also received the same name (fig. 28). There is not much resemblance between these two pictures and the latter is probably some affection of

FIG. 28.—So-called hole at the macula.

the choroid, either of an inflammatory or vascular nature. We therefore never know what to expect in a paper bearing this title.

Coloboma of the macula is another term to be considered under this heading. Obviously it means nothing, since one cannot have a coloboma merely of a region. But it may be said that this is intended to refer to a coloboma of the choroid at the macula. The characteristic features of a typical coloboma are shown in this drawing (fig. 29). However large the area involved there is only deposit of pigment round the edge, indicating where the normal choroid ceases. Had it been a large inflammatory scar there would have been far more pigment proliferation in the neighbourhood and not only round the edge, although it might be rather denser in this position. If we apply these principles to a coloboma of the choroid in the macular region we find something like the picture in fig. 30, namely pigment confined to the edge, with a pearly-white base and, in my opinion, quite unlike a choroidal scar. But the picture in the next drawing also has, however, been called a coloboma of the macula (figs. 31 and 32) and here we see gross pigment proliferation accompanied by the formation of fibrous tissue. There is not much similarity between this and the condition shown

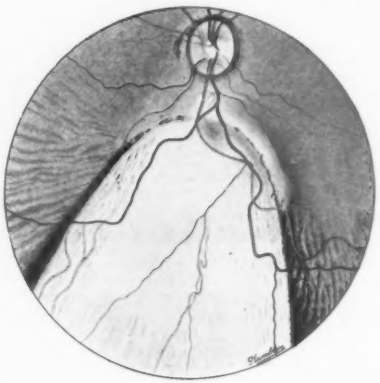

FIG. 29.—Coloboma of the choroid with more pigment.

in figs. 29 and 30. Figs. 32 and 33 appear to me to be far more suggestive of an old inflammatory choroidal scar, and the well-defined rounded border is, I think, characteristic of intra-uterine inflammations of the choroid in the fœtus.

The point to which I take exception in connexion with this particular lesion is, however, that the term " coloboma of the macula " is sufficiently vague to enable those who wish to do so to represent this type of so-called coloboma as a developmental epiblastic defect, and to utilize it in this sense in order to link it up with other epithelial diseases of the retina and describe the whole group under the heading of " epithelial abiotrophies ". The fact that an old inflammatory scar of this character has been found in members of the same genealogical tree seems to me of sufficient interest in itself to merit investigation without making out the defect to be of epiblastic origin.

DIFFERENT NAMES APPLIED TO THE SAME PICTURE

Then we come to cases where different names have been applied to explain exactly the same picture with similar pathological changes.

I have already referred to striate choroiditis in this connexion. I have, however, also found a paper with the title " angiopathia retinæ traumatica " but after seeing the picture and reading the text I find it corresponds exactly with what is known as commotio retinæ, a condition following a direct blow on the eye, which is said to have

been first described by Purtscher in 1910, though I think cases must have been noticed earlier than that. The disturbance in this case (fig. 34) is not at the macula but a little distance away from it, above the disc, but this is merely a

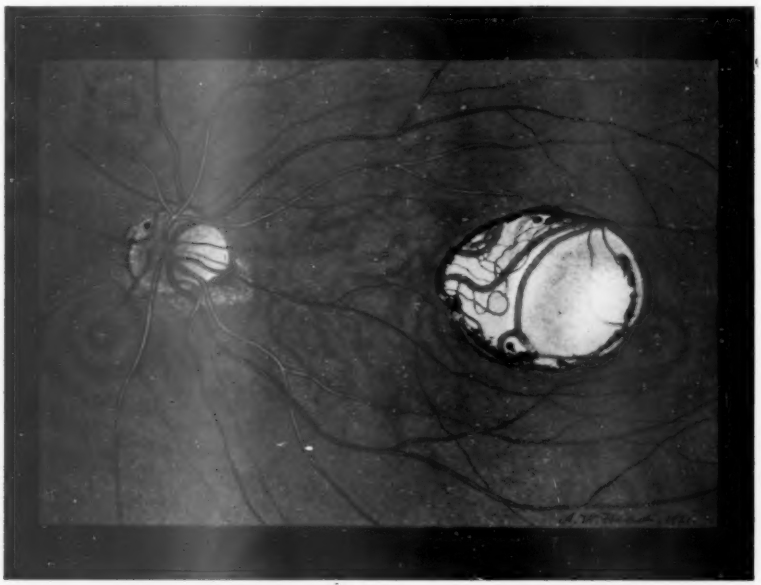

FIG. 30.—Coloboma of the choroid at the macula.

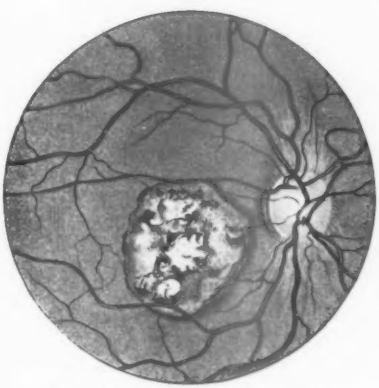

FIG. 31.—So-called coloboma of macula.

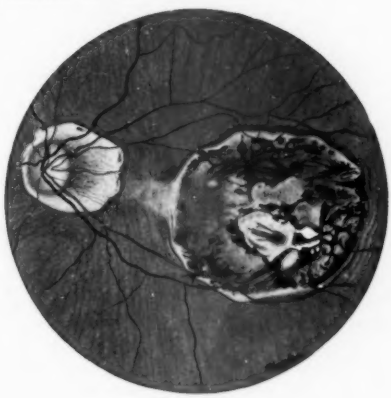

FIG. 32.

variation. This has also been called Berlin's œdema which is usually the first stage in a trauma of this character involving the retina and choroid.

When, however, I look up Purtscher's original paper and also other cases of angiopathia retinæ traumatica I find that the fundus pictures do not correspond with

what we understand by commotio retinæ, and that in some an entirely different state of affairs is seen ; nor is the clinical history the same. I now show some drawings described as belonging to this group. The changes seen have occurred in patients who as a result, e.g. of a fall or bad motor accident, have sustained serious injuries to various parts of the body, including the head, but without any evidence that the eye itself has been struck. Here is Purtscher's case (fig. 35) from the eye of a boy who fell off the roof of a house and had a fractured base of the skull, and here are others (fig. 36), all of which were found in the eyes of patients injured in motor crashes. They all represent the effects of rupture of the retinal vessels ; but in one other case which I found included in this category there were small hæmorrhages and exudates along the course of the larger retinal vessels and round about the macula which were very similar to the changes seen in renal or vascular retinitis. At the same time angiopathia retinæ traumatica is not a bad name for this condition. On the other hand we have by no means sufficient proof that what we call " commotio retinæ "

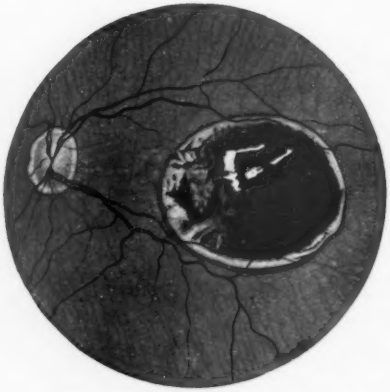

FIG. 33.—So-called coloboma of macula.

FIG. 34.—Angiopathia retinæ traumatica (commatio retinæ).

resulting from a direct blow on the eye, *is* a condition caused by injury to the retinal vessels because they are generally found quite normal, and also because of the migration of pigment which takes place and which can only occur when the choroid, pigment epithelial layer, and the external limiting membrane, are damaged. I think the term commotio retinæ should certainly be discarded, and another name substituted for it.

Post-retinal exudates, particularly of the grosser forms, and often situated at the macula, have received a variety of names. I have already mentioned one under the heading of " degenerations " ; but others are " sickle-shaped degeneration of the posterior pole of the eye ", " histology of submacular senile pseudotumours ", " transudative pigmentary choroido-retinitis ", and " senile macular exudative retinitis ".

There is nothing in all these terms to indicate that the conditions are in any way alike, except in the position they occupy at the macula, but on looking up the papers

and after reading the contents, I find that the histological and pictorial descriptions are essentially the same and show pathological changes usually found in all large post-retinal exudates, with only slight variations such as that of a little blood or pigment finding its way here and there through the albuminous fluid to the surface.

I hope I have now said enough to convince you of the desirability of a complete re-examination of the whole subject, if this is in any way possible.

I suppose, however, that I must not stop here, or I shall lay myself open to the well-known criticism which has been levelled against the ten commandments, viz.: "They don't tell you what to do, and only put ideas into your head." If I have only put ideas into your head I shall be satisfied, but I am quite alive to the fact that to enter upon the task of drawing up a new nomenclature of diseases of the fundus

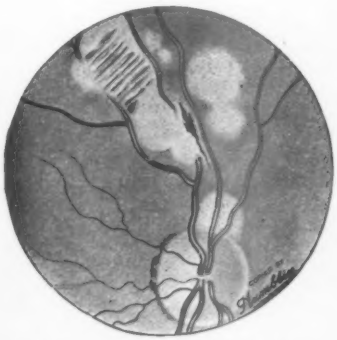

FIG. 35.—Purtscher's angiopathia.
(*Archiv f. Ophthal.*, 1912, **82**, 347.)

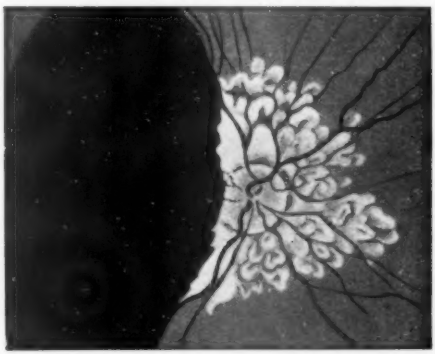

FIG. 36.—Angiopathia.
(Amsler, *Annales d'oculistique*, 1934, **170**, 568.)

acceptable to everybody would be a stupendous undertaking, and one involving international co-operation.

I will, however, make the following suggestions :—

(1) Since the choroid and the retina are the parts concerned, let us describe all diseases of the fundus, if possible, in terms of one or other—or perhaps both—of these structures, and include all details seen in the picture in one pathological whole, in the same way that we speak of thrombosis of the central vein of the retina.

(2) This may not be possible for two reasons :—

(*a*) Because there may be more than one pathological condition existing at the same time ; but in spite of this the nomenclature can follow the same lines.

Fig. 37 shows pigmentary degeneration of the retina at the macula, hyaline degeneration of the membrane of Bruch and a choroidal hæmorrhage, all in one picture.

(*b*) Because the condition is a very rare one or the pathology is not known, in which case we cannot escape the necessity for resorting to a pictorial description ; or we may put it in a non-committal pathological form (e.g. " retinal folds ", " post-retinal exudate, or hæmorrhage ", &c.).

(3) When we are obliged to employ a pictorial name let it be one as simple as possible (with an explanatory note if it is not in English), easily comprehensible to everyone and in a useful form for purposes of reference and classification.

(4) Before making a diagnosis it is important to take account of the clinical history. The following two cases illustrate the necessity for considering this point, and for

not judging by the picture alone. Fig. 38 shows ordinary senile pigmentary degeneration of the retina at the macula. Fig. 39 shows pigmentary degeneration of the retina in a case of amaurotic family idiocy.

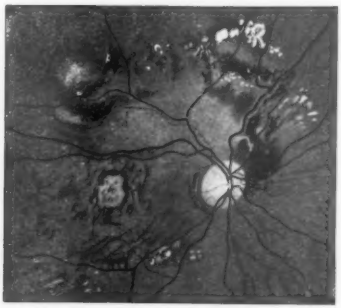

FIG. 37.—Three different conditions in one eye.

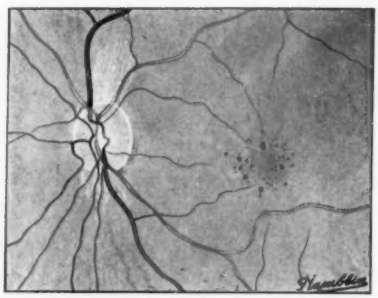

FIG. 38.—Pigmentary degeneration of retina at macula in patient aged 82..

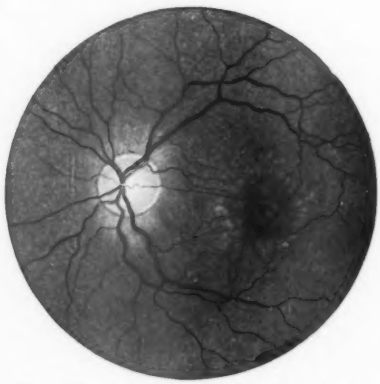

FIG. 39. — Early case of pigmentary degeneration of retina at macula. Familial macular degeneration.

Further than this I am not prepared to go at the moment, but this may serve as a guide to those interested in the subject.

Acknowledgments and thanks are given to the authorities by whose courtesy the illustrations mentioned below have been included in this paper :—

Figs. 1, 14, 20, 30, 32, 33 and 34, from the *British Journal of Ophthalmology*.

Fig. 2 from " Developmental Abnormalities in the Eye ", Cambridge University Press.

Fig. 3 from the *Archives of Ophthalmology*.

Fig. 4 from the *Royal London Ophthalmic Hospital Reports*.

Figs. 5, 10, 11, 13, 16 and 28, from the *Transactions of the Ophthalmological Society of the United Kingdom*.

Figs. 21 and 36, from *Annales d'Oculistique*.

Fig. 35, from *Archiv für Ophthalmologie*.

Thanks are also due to Messrs. Adlard and Sons, Messrs. G. Pulman and Sons and the Cambridge University Press, for the loan of blocks.

Section of Therapeutics and Pharmacology

President—J. W. TREVAN, M.B.

[*October* 11, 1938]

WALTER ERNEST DIXON MEMORIAL LECTURE

Resistance to Experimental Cancer

By Sir FREDERICK G. BANTING, K.B.E., F.R.C.P., F.R.S.

IN 1925 I visited the laboratory of Dr. W. E. Gye, and since that time my main interest in medical research has centred in the cancer problem. With the assistance of Miss S. Gairns, many experiments have been performed in the laboratory, and I would like to report some of these in this paper.

Introduction.—Although at present there is nothing to offer in the way of a specific therapeutic agent to the patient suffering from cancer, progress to this end has been made.

Many authors have referred to the phenomenon of " Resistance to Experimental Cancer " as " immunity ", but until it has been finally proved that cancer in general is due to a virus or living agent, it is probably better to use the term " resistance ". In the case of the filtrable fowl tumours which have been shown to be due to a virus, it is permissible to use the term " immunity ".

The earliest workers on experimental cancer observed the regression of tumours, and the subsequent resistance to further transplantation, and sought by experimentation to find the cause of the regression with the idea of clinical application. Probably no aspect of the cancer problem has received more consideration and prompted more experiments. Woglom in 1929, in his review of the literature, discussed over 600 papers, most of which were published since 1913. Many important papers have appeared since 1929. Hence a comprehensive review of the literature is impossible.

Before 1903 workers in isolated laboratories had made observations on tumours in animals, especially in mice, and had transplanted fragments of the tumours into other mice, and thus carried the tumour strain, but it was not generally accepted that these scientific curiosities had a very close relation to the tumour problem in man.

In 1889 Hanau described the first successful transplantation of carcinoma within the same species, and two years later Morau (1891) reported a carcinoma which had been carried through seventeen generations of transplants, over a three-year period. Jensen, Loeb, and Borrel, made extensive observations on experimental tumour, and as early as 1901 Jensen reported the spontaneous regression of a tumour in a mouse.

With the establishment of the Imperial Cancer Research Fund, coördinated research on cancer was begun, and it is to the men that formed the original group and to their successors, that the world will always owe a deep debt of gratitude. They first established the fact that cancer is fundamentally the same in all animals and in man. They studied many strains of transplantable tumours in many different species of animals, and their observations form the basis for much of the subsequent research on cancer.

In 1906 Bashford, Murray and Cramer reported their investigations into the natural and induced resistance of mice to the growth of cancer. They showed that animals

in which tumours had developed and then had been absorbed were highly refractory to further inoculation. Animals in which a tumour had disappeared, following exposure to radium, were refractory in the same way and to a similar degree as those in which absorption had occurred spontaneously. They found further that although protection was absolute for the tumour strain recovered from, it was not necessarily absolute for other tumours. They thus suggest a specificity in the protection.

Bashford, Murray and Haaland carried out extensive experiments on the induction of resistance to transplanted tumours by preliminary injection of normal tissue cells such as red blood-cells, mammary gland, skin and embryo, and found that by this procedure a varying degree of resistance to transplantation might be produced. These results were obtained only when living tissues of the same species were used throughout the experiment.

When a tumour transplantation is made into a susceptible animal, the peripheral parenchymal cells live, but the central cells and the stroma of the graft die. Russell studied the fate of grafts placed in resistant mice and found that for the first two days the changes were the same as those observed in normal mice, but that on the third and subsequent days there was a marked difference. The host fibroblasts did not penetrate the implanted fragment, there was no stroma formation, and in place of vascularization and growth there was a shrinkage of the necrotic centre and a cleft formed between the cells of the tumour and the host. The thin peripheral layer of tumour cells thus formed a cystic cavity which persisted for some days, and was not completely absorbed until from twelve to fourteen days had elapsed. Woglom, using Flexner-Jobling rat adenocarcinoma, confirmed these findings.

Russell then carried out his important experiments on " concomitant induced immunity ". Various strains of tumour were transplanted into mice (in one flank) and, after about two weeks' growth, were surgically removed. Two or three days later the same, or different, strains of tumour were transplanted into these mice—in the opposite flank. Russell found that the growth of some strains, notably 63, did not confer noticeable resistance to subsequent transplantation, while the growth of other strains, notably 206, would render mice highly resistant not only to 206, but also to many other strains, including 63. He thus showed that certain strains of tumours by their growth in an animal, confer resistance against tumour. This he called " concomitant induced immunity ".

The early experimental work on mammalian tumours—mostly in mice and rats—demonstrated clearly that tumours in animals were identical with tumours in man in respect of mode of origin, age incidence, clinical course, mode of growth and infiltration of surrounding tissues, and formation of metastases. Transplantation could only be carried out within the species. There was strict specificity. The daughter tumours were derived entirely from the cells of the implanted graft. Tumours could only be propagated by means of the transplantation of living cells.

Until 1909 these constituted the most important facts concerning the knowledge of experimental tumour and resistance to tumour. During the next decade, however, the work of Rous and his associates on virus-induced tumours and the work of Yamagiwa and Ichikawa on chemically-induced tumours, was destined to change the course of investigations. The latter workers induced tumours in rats and mice by repeated application of tar to the skin. Tar tumours can be transplanted only within the species and only by means of the living cell. Kennaway and Cook in England, and Fieser in the United States, have made extensive investigations of the chemical aspect of this problem, the outstanding feature of which is the variety of chemical agents that will induce tumour, and the fact that once the tumour is induced the chemical agent no longer operates in perpetuation of the growth. From the aspect of resistance, therefore, the chemically-induced tumours do not differ from mammalian tumours.

In 1910, however, Rous, Murphy, and Tytler, working in the Rockefeller Institute, found, among fowls, a number of sarcomas which could be propagated by means of a cell-free filtrate. At first, most pathologists thought that these tumours were due to inflammation and were not true sarcomas, but as a result of further investigation they are now generally considered to be true cancers. Rous sarcoma No. 1, as the most important strain is now called, is one of the most universally used laboratory tumours. It was with this tumour that Gye did most of the work on which he based his virus-specific factor. It is caused by a virus by means of which it can be transmitted from fowl to fowl. It thus differs from the formerly known mammalian tumours which required the transfer of living cells for the formation of a new growth. Yet in every other way—e.g. marked species specificity, malignant invasion of normal tissues, and metastases—the Rous sarcoma is identical with mammalian tumours.

Rous found that certain growing tumours regressed and that the bird was subsequently resistant to tumour growth. He injected the serum of resistant birds into tumour-bearing birds, but found no alteration in the growth of the tumour in the treated animals.

Mottram found that when Rous tumours were made to regress by means of the application of radiation, some birds were immune to subsequent tumour inoculation.

Resistance to Rous Chicken Sarcoma.—Since 1926, a study of Rous sarcoma has been made in our laboratory using pure-bred Barred-Rock fowl obtained from the Ontario Agricultural College. The birds used were fully-grown chickens from 6 to 12 months old. Younger birds were used during the spring months of certain years. The age of the bird is an important factor, because in young birds Rous sarcoma develops more readily than in old ones and kills more rapidly. Gye used young chicks, and reported that in 6,000 birds he found only one in which a tumour regressed.

In order to have a constant supply of tumour tissue for experimental purposes, transplantations into from three to six normal chickens were carried out every week. Transplants were made into the muscle of both breasts with a trocar of about 2 mm. diameter. When tissue was required for experiments or transplantation, the chicken with the most rapidly growing tumour was killed, and thus the birds with the more slowly growing tumours were allowed to survive.

In the six-year period 1928 to 1934, 1,768 chickens were transplanted. Of these 621 were killed to supply tumour tissue; of the remaining 1,147 birds, 1,140 died of tumour and seven—that is, one in 164—became resistant to Rous sarcoma. A resistant bird is one in which a well-established tumour regresses; on additional transplantation a second small tumour may develop, which also regresses. The bird does not develop tumours on subsequent transplantation with the cells of the tumour to which it is resistant, and it does not die of tumour.

During the past ten years we have used approximately 6,000 fowls for experimental work on Rous tumour and of these 118, or approximately one bird in 50, has shown some degree of resistance. Of the 118 birds there were 44 birds which received more than five direct transplants and remained negative following regression of the first tumour. Some of this group were kept in the laboratory as long as five years, during which time they received upwards of 40 transplants. Thirty-eight of these birds have died and at autopsy showed no sign of tumour. Six are still alive and well. In addition, there were 15 birds which remained negative following two or more transplants. Four birds of this group are alive; the other 11 birds showed no sign of tumour at autopsy.

Thirteen birds remained negative to cell-free tumour extract on repeated occasions but developed tumours and died following the inoculation of Rous cells. A fowl may therefore be resistant to cell-free filtrate but not to transplanted cells. In 20 birds a tumour of large size regressed, but on subsequent transplantation the bird again developed a tumour and died. One bird, for example, had in all, five large tumours

over a period of two years. Four of the tumours regressed but the bird died as the result of the fifth. Five birds lost their resistance to tumour and died bearing a large tumour. An example of this was a bird (No. 4172) which had received two injections of tumour extract, and 21 inoculations of Rous cells, between November 1, 1933, and March 10, 1936. Following the twenty-second transplantation of cells a large tumour developed which caused the death of the bird. The remaining 21 of the 118 birds may be classed as "partially resistant." They have died of tumour. Some of this group have had a tumour develop and regress following many transplantations. Some birds have had a very slow-growing tumour in one breast and have been resistant to the injection of tumour extract or to the inoculation of cells into the other breast. Instances have been observed where a large tumour in one breast had almost disappeared when the direct transplant or an injection of tumour extract into the opposite breast caused a rapid growth of the original tumour. There is thus a very marked variation in the degree of resistance among fowls.

From the very earliest work on transplantable tumours it was observed that the size of the transplant had an important bearing on the result. Purdy has emphasized this point again in the growth of Fujinami tumours in adult ducks. It was thought, therefore, that a tumour might be produced in a resistant bird by the administration of a large dose of active tumour cells. On August 1, 1933, bird No. 373 was given 6 c.c. of finely divided tumour cells in the breast muscle. This dose was estimated to contain sufficient tumour-producing substance to kill 5,000 birds. The bird developed a tumour which in eight days measured 1·4 by 3·5 cm. Two weeks later the mass had entirely absorbed and the breast was quite normal. Thus a highly resistant bird can overcome the growth activity of enormous numbers of active tumour cells.

Regression of Animal Tumours.—The manner in which regression occurs in a Rous sarcoma varies with the type of tumour. The slow-growing, firm, fibrous tumour regresses slowly, becoming smaller and smaller, until it has entirely disappeared, leaving soft, normal muscle. A rapidly-growing, soft, cellular tumour usually develops a line of demarcation between itself and the muscle; it then begins to shrink in size; the overlying skin, which is usually red, shining, and stretched, regains its normal appearance. The tumour may gradually separate from the muscle and form a cyst which usually persists for many months before it is absorbed. Sometimes it would appear that the cells of a rapidly-growing tumour simply die in mass. The dead tumour becomes a dry, black, desiccated mass which, like a foreign body, is ulcerated through the skin and extruded.

As is frequently stated, a tumour-bearing animal does not die of the actual healthy growing tumour, even though the mass may be almost the size of the animal. Death is caused by infection of the tumour, ulceration, or the invasion of essential internal organs—heart, lungs, or liver—with secondary growth, or by the toxins absorbed from extensive necrosis of the tumour cells. When large amounts of waste products of breaking-down tumour are being absorbed, the bird loses weight, and is pale and inactive. One of the first signs of regression is often found in the appearance of the bird. The comb becomes red, the bird gains in weight and becomes active, even though the tumour is still quite large.

Woglom has investigated the histology of regressing tumours in the rat using the Flexner-Jobling tumour. He first found that if two transplants are inoculated at the same time, either both progress or both regress. He therefore transplanted tumour tissue into rats, in both flanks, and removed one of the transplants at varying intervals, leaving the other in the animal, for observation. In this manner he was able to obtain tumours at the period of beginning regression. On histological examination he found that the peripheral cells of the tumour, or in other words, the cells in most intimate contact with the host, were the first to degenerate. The death of the tumour was from without inward. This would seem to be the case in rapidly-

Neutralizing Effect of Rous-resistant Plasma on Rous Sarcoma Extract in Vitro.—growing Rous tumour because of the separation and cyst formation, but histological studies have not been made.

Very early in the investigation (June 1930) it was found that the plasma of Rous-resistant birds neutralized the cell-free active filtrate of a Rous tumour. The plasma of a resistant bird was mixed with tumour extract, incubated at 37·5° C. for one-half to three hours and injected into each of three birds. No tumours resulted. Normal bird plasma tested in the same manner had no such neutralizing effect. Over forty experiments of this nature have been carried out. Whereas in the early experiments 2 c.c. of resistant plasma were used to neutralize 1 c.c. of tumour extract, in later work as little as $\frac{1}{10}$ of 1 c.c. or less, completely neutralized 1 c.c. of potent extract. This is probably due to the hyperimmunity developed in resistant birds as a result of repeated tumour-cell inoculation.

Rous treated five tumour-bearing birds with a single transfusion of from 35 to 60 c.c. of blood from resistant birds, but the tumours grew quite as well as those of untransfused controls. We repeated this experiment on two occasions when we had 15 resistant birds. Blood was drawn from these once a week and their mixed plasma used for treatment. Incubation tests showed that 0·1 c.c. of this mixed plasma completely neutralized 1 c.c. of potent tumour extract.

In the second experiment one normal bird was given 1 c.c. of tumour extract and eleven days later, when the tumour measured 2 by 2·2 cm., resistant plasma treatment was begun. The bird was given 15 c.c. twice daily during the first week and 10 c.c. daily during the second week. In this way 283 c.c. of resistant bird plasma was administered, but despite this large amount the tumour increased rapidly in size and the bird died in thirty days with a large breast tumour and metastases in the lungs.

From the fact that large amounts of highly immune plasma had no effect on the growth of a tumour, and from the experiments of Fischer, it would appear that the virus, being within the cancer cell, is not affected by the antibodies of the blood. Fischer grew Rous cells in tissue culture and to the culture media he added the serum of a bird which had been resistant to five Rous transplants. He carried his tissue cultures through thirty generations over a period of two and a half months, at the end of which time the cells were inoculated into a bird and produced a tumour.

Sac Grafts in Rous-resistant Chickens.—When Rous cells are injected into a resistant bird the cells die and are absorbed. The question is: Do these cells die from lack of blood supply, or are they actually killed by the antibodies of the blood? In order to throw some light on this question, fragments of Rous cells, of the size generally used for transplantation, were placed in sacs made from fresh hen peritoneum. In some cases the hen peritoneum was treated with silver salts and thoroughly washed. These sac grafts were placed in the breast muscle of resistant birds and removed at intervals up to ten days. On removal they were immediately grafted into the muscle of normal birds. Of 20 sac grafts which had remained in resistant birds for more than forty-eight hours, only one produced a tumour. Of the six sac grafts which were removed from resistant birds in forty-eight hours or less, only two produced tumours when placed in normal birds. From these experiments it would appear that the concentrated immune serum which bathed the cells in such a graft had a lethal effect on the tumour cells. The point as to whether or not the cell membrane can afford absolute protection to the virus against immune serum is an important one and requires further investigation.

Neutralizing Effect of Rous-resistant Plasma on Rous Sarcoma Extract in Vivo.—Since the administration of immune plasma to a bird had no effect if the tumour was well established, it was decided to give the plasma at the same time as the tumour inoculation. Tumour extract was mixed with immune bird plasma and injected immediately. It was found that one or two of the three birds so injected always

developed a tumour. Hence it appeared that immune plasma required time for the neutralization of the virus.

When cell-free tumour extract was administered intravenously through a fine needle and washed in with saline, no tumour developed unless there was a foci of inflammation or vascular disturbance as, for example, in the ovary of a laying hen. This observation was used in order to ascertain whether or not the neutralization of tumour extract by immune plasma could be made to occur *in vivo*. Nine birds were each given 1 c.c. of a dilute solution of turpentine (1 : 40) in the right breast. The following day three of these birds were given intravenously 10 c.c. of a mixture of equal parts of immune plasma and tumour extract that had been incubated for three hours at 37·5° C. The next three birds were given intravenously 10 c.c. of a mixture of equal parts of normal bird plasma and tumour extract incubated three hours at 37·5° C. The last three birds were given intravenously 5 c.c. of resistant bird plasma and 5 c.c. of tumour extract through the same needle from different syringes.

The normal serum control birds all died of breast tumours. The birds which received the non-incubated, unmixed immune plasma and tumour extract all died of breast tumours, while no breast tumours developed in birds receiving the incubated resistant plasma and tumour extract mixture. One of these birds developed a tumour on the wing at the site of injection.

This experiment indicated that the neutralizing effect of the immune plasma occurred in the test tube during incubation and required time for the inactivation to occur.

Rous-resistant Plasma as a Prophylaxis to Development of Rous Sarcoma.—Experiments were carried out to ascertain if fowls could be protected against tumour by means of resistant bird plasma. Three birds received 30 c.c. of plasma during the week before receiving an injection of 1 c.c. of tumour extract. Each bird received three doses of 10 c.c. of the resistant plasma in breast muscle. None of the birds developed tumours. A group of six birds were treated with 20 c.c. of resistant bird plasma for six days before receiving tumour extract. Each bird received three doses intraperitoneally. Only one bird developed a tumour, and this killed it in forty-nine days. The remaining five birds received a second dose of tumour extract three weeks later and all died of tumour. It was found, however, that smaller doses of plasma did not protect the birds against tumour extract. When 10 c.c. of plasma were given 12 birds out of 15 developed tumour.

From these experiments it will be seen that it was necessary to give approximately 30 c.c. of resistant plasma in order to protect a bird against the injection of 1 c.c. of potent tumour extract. This is a relatively large amount; in a test tube this same amount of plasma would more than neutralize 300 c.c. of the same extract. Therefore, it appeared that the plasma, when injected into the body, was diluted by the body-fluids and blood, and unless large quantities of serum were given, there was not sufficient concentration at the site of inoculation to bring about the neutralization and protection of the local cells.

Four birds were treated with immune plasma for a week before tumour-cell transplantation. Each bird received 20 c.c. intraperitoneally, in three doses. All the birds developed tumours and died within twenty-eight days. Here again is seen the difference between extract and cell, resistant plasma being ineffective against the growth of cells.

All tissues of a resistant bird appear to be resistant both to cell-free filtrates and to Rous tumour cells. Two resistant birds were each given an intravenous injection of 3 c.c. of a very finely chopped suspension of Rous cells. The birds did not die, nor did they show any evidence of metastases. Control birds receiving 1·5 c.c. of the same suspension died in thirteen and sixteen days, respectively, with multiple tumours in internal organs, especially in the lungs.

Extracts were made from fresh tissues of two resistant birds. It was found that

extracts of liver neutralized tumour extract as completely as resistant serum ; extracts of muscle and kidney were less effective but showed some evidence of neutralizing effect—one out of three birds developing a tumour.

Resistance to Fujinami Tumour in Chickens.—Since 1933 we have also had available for study the Fujinami tumour, a myxo-sarcoma which was originally discovered in a chicken but which can be propagated in both chickens and ducks.

In our experience the Fujinami tumour showed a much greater tendency to regress, and thus to confer resistance, than did the Rous. Pure-bred Barred-Rock birds were used as in the case of the Rous tumour. During the course of all experiments 180 birds were used. Of these 158 died of tumour or were killed in order to obtain Fujinami tumour cells, while 22 fowls showed some degree of resistance : that is, one bird in eight, as compared with one bird in 51, in the case of Rous sarcoma. Twelve birds that were resistant to Fujinami tumour-cells were inoculated with Rous extract or cells. Ten of these birds developed Rous tumours and died, while two became resistant to Rous tumour. Although Fujinami tumour has not been studied as extensively as Rous tumour, it would appear that there is a similar variation in the degree of immunity in the two tumours. Thus there are birds in which tumours do not develop following the injection of Fujinami tumour extract but in which tumours develop following the injection of cells. Regression of one tumour does not always prevent the development of another tumour on subsequent transplantation.

Development of Fujinami Tumour and Dibenzanthracene Tumour in Rous-resistant Chickens.—In order to ascertain whether a bird which was resistant to Rous sarcoma would also be resistant to Fujinami tumour, two of our Rous-resistant birds (Nos. 373 and 1038) were given an extract of dried Fujinami powder. Chicken No. 373 had been under observation for three years, during which time it remained negative to seventeen direct transplants of Rous sarcoma. Chicken No. 1038 had been under observation for over two years and had remained resistant to eleven Rous transplants. Both of these birds developed large tumours following the Fujinami inoculation and died with secondaries in the lungs, in thirty-five and forty-nine days respectively. Blood was obtained from the heart of bird No. 373 at autopsy and the plasma was found to completely neutralize Rous tumour extract. Plasma of bird No. 1038 obtained within twenty-four hours of death, also neutralized Rous extract. This would indicate that these birds remained resistant to Rous sarcoma although dying of Fujinami tumour.

It was also found that plasma of a Fujinami-resistant bird neutralized Fujinami cell-free extract but did not neutralize Rous extract. Conversely, plasma of a Rous-resistant bird neutralized Rous cell-free filtrate but had no effect on Fujinami extract.

Twelve Rous-resistant birds and 12 normal birds were each given three injections of 5 mgm. of 1.2.5.6-dibenzanthracene in lard into the breast muscle at fortnightly intervals. Four of the 12 resistant birds were given Rous transplants at intervals throughout the experiment and it was found that they remained negative to Rous. Eight of the 12 normal birds developed dibenzanthracene tumours, three remained negative and one died in four months from other causes. Six of the Rous-resistant birds developed tumours and six remained negative. At autopsy the tumours of the Rous-resistant birds were characteristic of dibenzanthracene. This was confirmed by histological section. Thus it may be concluded that a high degree of resistance to Rous does not protect a bird against the development of a dibenzanthracene tumour.

The Rôle of the Monocytes in the Development of Tumours.—Rous tumour is always the same, whether it is produced by the inoculation of cells or of cell-free filtrate. Hence it is important in the study of immunity to know the type of cell in which the virus grows. Carrell believed that the monocyte gave rise to Rous tumour and reported that chicken monocytes, grown in tissue culture, could be transferred into tumour cells by the addition of Rous virus to the culture media. Ludford was unable to confirm this finding but was able to produce Rous tumour

in vitro by growing chicken fibroblasts in culture media to which Rous cell-free extract had been added.

Of all the blood-cells, monocytes alone wander out into the alveoli of the normal lung; hence it was thought that if tumours arise from monocytes, tumour extract introduced into the lung should produce a tumour. Accordingly, by means of a soft rubber catheter, 1 c.c. of a potent tumour extract was introduced at the level of the bifurcation of the trachea. In four experiments 14 out of 15 birds died of massive lung tumours. Kaolin had been added to these extracts. In three experiments tumour extract without the addition of kaolin was administered, and four out of 12 birds developed lung tumours. Multiple tumour foci were seen scattered throughout the lung as early as six days after the introduction of the tumour extract to which kaolin had been added. These experiments indicate that the monocyte takes up the virus and carries it into the lung tissue. The histological appearance of the early miliary tumours of the lung would suggest that the monocyte was the cell that underwent malignant transformation.

Neutralizing Effect of Tumour Exudation.—In the periodic examination of birds with growing tumours we sometimes encountered an exudation of fluid under the skin overlying the tumour. The tumour was always of the more slowly-growing type. On a number of occasions the fluid was drawn off and it was found that it did not give rise to a tumour when injected into other birds, but, on the other hand, it had a neutralizing effect equivalent to that of resistant serum when added to tumour extract. Three of such tumour-bearing birds were studied extensively. Two of the birds died of tumour and it would appear that the tumour cells of these birds, although constantly exposed to immune serum, were not affected by it, because the virus was within the protecting cell. In the other bird the tumour regressed and the bird became resistant to six injections of tumour extract. It then received a direct transplant which resulted in a tumour which regressed. Following this it was resistant to ten direct transplants and died without a tumour.

Attempts to Produce Resistance to Rous Sarcoma.—We have made many attempts to immunize fowl to Rous sarcoma. Following the principle of the toxin-antitoxin mixture used so extensively, we have given birds repeated injections of neutralized or partially neutralized serum-tumour extract mixtures. An example of one of the early experiments is as follows: Once a week, for five weeks, ten birds were each given 1 c.c. of tumour extract neutralized with resistant serum. Four weeks later each bird was given 1 c.c. of unneutralized tumour extract. Six of the 10 birds developed tumours and died. Of the other four, two became resistant and two partially resistant.

The procedure was modified and many experiments were carried out, but the difficulties could not be overcome. If too much serum was added there did not appear to be any immunity produced; if too little serum was added the injection resulted in a tumour which killed the bird. It was impossible to predict the potency of a tumour extract, consequently the amount of serum necessary to neutralize it could not be calculated.

Owing to the many failures to produce with constancy even minor degrees of resistance to Rous sarcoma, it was thought that the production of resistance might be connected with the tumour-cell itself. The object was to kill the tumour-cell by physiological means so that the hypothetical antigenic properties might remain. For this purpose it was decided to use ammonia, since that is a by-product of cell metabolism. The procedure was as follows: Tumour tissue was ground through strong cotton, which gave a fine suspension of cells. Ammonium chloride and ammonium carbonate solutions were made (2, 5, 10, 15, and 20 grm. per 100 c.c.). In order to obtain a neutral solution, one part of ammonium carbonate and nine parts of ammonium chloride were used. Tumour cells were added to ammonia

mixtures of varying percentages, shaken for four hours, and recovered by centrifugation. It was found that the cells thus treated, even when 20% ammonia was used, gave rise to a tumour when injected into normal birds. This was surprising, since it was found that Balogh mouse sarcoma cells were killed when treated with 1% ammonia solutions. Suspensions of Rous cells were treated with ammonia and then exposed to immune plasma. However, no resistant birds were produced by any of these procedures.

In 1925 Vallée, Curré and Rinjard produced immunity to foot-and-mouth disease by the injection of the virus killed by exposure to low concentrations of formaldehyde. Since that time it has been found that formaldehyde removes the toxicity and kills other viruses without altering the specific antigen.

Mendel found that glyceric aldehyde, which has the same aldehyde group of molecules as formaldehyde, prevented aerobic glycolysis of tumour slices in the Warburg apparatus. Glyceric aldehyde, being a three-carbon sugar, has the added advantage that it can be administered intravenously or intraperitoneally. We attempted to immunize birds to Rous tumour by injecting them with tumour cells which had been treated with glyceric aldehyde. The tumour tissue was reduced to a fine pulp by grinding it through strong cotton. The cells were suspended in a 0·4% solution of glyceric aldehyde and shaken at intervals for three hours; they were recovered by centrifugation, suspended in normal saline. Six birds each received 2 c.c. of this suspension. Three developed tumours and died in the usual time. Two others developed tumours which regressed, but on retransplantation they died of tumour. The other bird did not develop a tumour; it also remained negative following the injection of two active tumour extracts, but on receiving a transplant it developed a tumour and died in twenty-five days.

Other experiments were carried out by giving birds repeated injections of Rous cells treated with glyceric aldehyde. 4% glyceric aldehyde was used for the first four or five treatments, and 0·4% for the later injections. It was found that the injection of cells treated in this way did not appear to promote the formation of antibodies against tumour. However, from the earlier experiments, when the cells were exposed to the dilute solutions of glyceric aldehyde, in some cases they produced a more slowly growing tumour from which the bird recovered. Birds with tumours were also treated with glyceric aldehyde but without effect. The results of the experiments with glyceric aldehyde were not sufficiently promising to warrant further work.

Resistance to Mammalian Tumours in Mice.—A study has also been made of resistance to mammalian tumours in mice. Tumour 63, C 180 and Balogh have been used, and it was found that spontaneous regression occurred with all these strains. During a two-year period 1,216 mice were transplanted with C 180. Of these 85 mice became resistant following the regression of the first tumour and died without a tumour, i.e. 1 in 14 mice became resistant. During a two-and-a-half-year period, 1,489 mice were transplanted with Balogh cells and 13 became resistant, i.e. 1 in 114 mice. This indicates that of all experimental mouse tumours the Balogh is possibly the most malignant and for this reason is comparable to the Rous tumour in chickens.

Many of the experiments which were carried out with chickens in an endeavour to produce resistance were modified and repeated with mice, using Balogh tumour—for example, the injection of cells treated with ammonia and with glyceric aldehyde. As was the case with the chickens, usually a small number of each group indicated that some degree of resistance had been produced, but for the most part the results were not satisfactory.

My colleague, Dr. Franks, is approaching the problem from an entirely different angle. He has sought to immunize mice against dibenzanthracene tumours by the repeated administration of dibenzanthracene which has been rendered antigenic by

linking it with a protein. These experiments are in progress but it is too early to predict the results.

Discussion

All the work on experimental tumour requires a large number of animals and a great deal of time. It is essential that control animals be used in all experiments, but, even with this precaution, there is such a great variation in the individual bird or animal that results are often difficult to interpret. The most outstanding feature of the cancer problem is the specificity of the disease. Cancer is identical in fowl, in mice, and in man, yet the disease cannot, with few exceptions, be transmitted outside the species. Resistance to cancer is even more specific.

The work to date unfortunately does not appear to contribute much toward a specific treatment for cancer. I believe, however, that a better understanding of the factors which produce immunity and resistance will ultimately lead to such a treatment.

The terms " immunity " and " resistance " are used in association, although, as was pointed out at the beginning of this lecture, the two words refer to different conditions. The term " resistance " is used to indicate refractoriness to the grafting of cells ; the term " immunity " to the condition under which an animal is able to combat, and possibly destroy, the intracellular agent which is known to be, for certain tumours, the proximate cause of the disease. The balance of evidence would lead most of us to conclude that the condition which I have called " resistance " is a laboratory phenomenon, unrelated to the realities of natural spontaneous cancer. It may be simply an indication of a reaction between host and tumour cell where there is a difference in genetic constitution of host and cell. If this were the complete explanation of the phenomenon of resistance we could scarcely imagine that the forces which destroy a transplanted tumour could ever operate in natural cancer, in which the malignant cells have necessarily the same genetic constitution as the host. It will have been observed, however, that with regard to some of the experiments which I have described, there lurks in my mind the notion that the forces which effectively rid an animal of a spontaneous tumour may be a combination of anti-cellular and anti-viral immune bodies. The spontaneous cure of natural cancer is very rare, but we have experimental tumours which can be propagated with cell-free filtrates and which are therefore the equivalent of spontaneous tumours, in that the tumours are composed of the host's own cells, and these tumours may, under certain circumstances, retrogress. As pointed out by Gye, the best example is the Fujinami tumour growing in ducks. When a relatively small dose of filtrate is injected into ducks, a tumour forms, grows rapidly, and almost always disappears. The less perfect example is the Shope rabbit papilloma which occasionally regresses. When regression of such tumours takes place the question arises whether the regression is brought about by the development of immune bodies which destroy the virus. Or is it a more complex process ? Kidd has investigated this problem. He has analysed by experimental methods the factors which determine the observed differences in the clinical progress of virus-induced papillomas and has shown that some are referable to the virus, some to the infected cells, and some to host influences. The interplay of these factors may determine either an unlimited growth of the tumour or its retrogression. He attributes self-cure of this tumour to a generalized resistance of host origin, elicited by and directed against the virus-infected cells. The opinion inherent in this work is that antigenic differences between host and malignant tissues may be sufficiently great to stimulate curative antibodies adequate to ensure the disappearance of even spontaneous cancers, and it is along these lines that the greatest hope for cancer therapy exists.